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Hormone replacement therapy – Current recommendations

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A B S T R A C T

Menopause is a major life event that can affect women in several ways. Its onset marks the end of the reproductive life cycle, and its impact can be both short and long term. Menopause is often a gradual process, preceded by a transitional period known as perimenopause. The average age of menopause in the UK is 51.

The clinical manifestations of menopause result from the eventual exhaustion of oocytes within the ovaries. This leads to a chronic hypo-estrogenic state, which in the short term causes menopausal symptoms and over a long term, has an impact on bone and cardiovascular health.

There has been a steep drop in the prescription of hormone replacement therapy (HRT) following the publication of the Women's Health Initiative Study and the Million Women Study. It is currently estimated that approximately a million women in the UK are taking HRT for control of their menopausal symptoms.

This review summarises the current recommendations for HRT use in menopausal women. The benefits of HRT in improving the symptoms of menopause are discussed as well as the potential role of HRT in managing long-term sequelae is covered. Evidence pertaining to the potential risks associated with HRT is also be reviewed.

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Hormone replacement therapy for the management of menopausal symptoms

Vasomotor symptoms

Hot flushes and night sweats are the commonest menopausal symptoms experienced by women and are collectively known as vasomotor symptoms (VMS). VMS can disturb sleep and can aggravate symptoms of tiredness, depressed mood, and anxiety. They may also be associated with palpitations [1,2].

VMS symptoms can predate the onset of menopause by a year or two, and it is thought that the mean duration of symptoms is just over 7 years, with a persistence of symptoms for up to 15 years in approximately 20% of women.

A Cochrane systematic review summarising results from 24 randomised control trials (RCTs), comparing oestrogen to placebo, showed significant improvement in VMS with oestrogen replacement and reported a 75% reduction in the frequency of hot flushes as well as an 87% reduction in severity with hormone replacement therapy (HRT) compared to placebo [3]. The NICE guideline network meta-analysis, found that transdermal HRT was more cost-effective than oral HRT for VMS, and was associated with a greater reduction in VMS severity with lower discontinuation rates [4].

Results have consistently shown that oestrogen replacement remains the most effective treatment for VMS. The decision whether to take HRT, the dose of HRT used, and the duration of its use, however, should be made on an individualised basis after discussing the benefits and risks with each patient, and arbitrary limits should not be placed on the duration of usage.

Non-hormonal interventions may be of help in women who have a contraindication to HRT or who do not wish to take HRT. These are discussed in detail elsewhere in this edition.

Mood

Perimenopause and menopause itself are associated with an increase in mood and depressive disorders. This is likely to be due to the interaction between oestrogen and the serotonin neurotransmitter pathway. Women with a history of premenstrual syndrome or postnatal depression appear to be at a higher risk.

Observational data suggest that the short-term use of HRT may improve mood and depressive symptoms during menopausal transition and in early menopause. Furthermore, randomised trial data have shown significant differences in mood symptoms associated with HRT, with 68–80% of women reporting decreased symptoms compared to 20–22% for those taking placebo [5]. Cognitive behavioural therapy can also be considered as a therapy option for the management of low mood and anxiety. It is important to refer women with severe depression for a formal mental health assessment and further management.

The progestogen component of HRT may negatively affect mood symptoms, and therefore, the type, dose, and route of administration may need to be modified to minimise this impact. Micronised progesterone is associated with fewer side effects than when compared to the more androgenic progestogens and may be more suitable for women reporting mood changes resulting from the progestogenic component of combined HRT.

Female sexual function

Many women experience sexual dysfunction during menopause transition, and this can result in a significant reduction in quality of life. Sexual desire and libido are a complex notion, which is impacted by several factors. While it is understood that there is a gradual age-related decline in sexual function including libido, arousal, and orgasm, there appears to be an acceleration of this decline seen around the time of menopause.

Systemic oestrogen replacement, as well as the introduction of systemic testosterone taken in female replacement doses, can improve overall sexual desire and libido. Topical vaginal oestrogen can improve the superficial dyspareunia associated with vulvovaginal atrophy (VVA), leading to a possible improvement in sexual function. The addition of testosterone supplementation to HRT can be

considered to improve symptoms of reduced sexual desire and arousal particularly if adequate systemic oestrogen replacement has not been found to be effective.

A recent global consensus position statement from leading menopause societies (2019) supported the use of testosterone therapy for the treatment of hypoactive sexual desire disorder (HSDD) in postmenopausal women with no significant adverse events when testosterone levels were maintained within the female physiological range [6].

Testosterone has been available as transdermal products (patches and gel) and subcutaneous implants. A number of these preparations have been discontinued for commercial reasons, and at present, there are no licensed testosterone preparations available for women in several countries, including the UK. As a result, testosterone preparations manufactured for use in men are used out of licence, with adjustments to maintain female physiological replacement doses.

A total of 1% testosterone gel is available in 50 mg and 5 mL sachets, and 2% testosterone gel is available in 60 mL canisters for male use. Off-license prescribing by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 mL/day, or one pump on alternate days, both equating to a daily dose of 5 mg/day. Alternate day administration, however, is likely to result in fluctuations in serum levels. A 1% testosterone cream (0.5 mL/day) with an indication for female use is manufactured in Australia and is only available privately at present in the UK.

Tibolone, which has some weak androgenic properties, can have a beneficial effect on mood and libido. Other options such as oral DHEA require further research to confirm their efficacy and safety.

While serum testosterone estimation is unhelpful in the diagnosis of HSDD, a baseline measurement prior to the commencement of treatment and then at regular intervals is recommended.

Androgenic side effects such as hirsutism and acne are rare, provided the free androgen index ((testosterone $\times$ 100)/sex hormone-binding globulin) remains within the female physiological range (<5%). Cardiovascular and cancer safety data have been reassuring to date, although there is a call for further long-term studies [7].

Vaginal symptoms

The vagina, lower urinary tract, and pelvic floor all share one embryological origin and, as a result, all contain oestrogen receptors. Following the oestrogen-deficient state of menopause, there is a progressive loss of collagen in tissue atrophy within these structures. Symptoms that can result are dyspareunia caused by VVA and urethral syndrome, the term collectively given to dysuria, urinary urgency, and frequency. These symptoms can have a significant impact on quality of life and can result in sexual dysfunction and relationship distress.

Topical vaginal oestrogen therapy provides effective symptom relief and improvement in the cytological composition and physiology of the vaginal epithelium. Oestrogen increases mucosal proliferation, thus increasing blood supply to the urogenital tissues and improving vaginal lubrication. Oestrogen therapy also appears to restore an acidic tissue pH by increasing lactobacilli dominance within the vaginal flora and can be effective in reducing the number of episodes of recurrent urinary tract infections in postmenopausal women [8].

Low dose topical vaginal oestrogens have been shown to be effective for the management of VVA. In addition, vaginal oestrogens have also been shown to improve sensory urgency compared to systemic preparations.

It has been shown that approximately 15–20% of women receiving systemic oestrogen without topical vaginal oestrogen replacement will continue to experience VVA symptoms related to oestrogen deficiency, and this is often significantly improved by the addition of topical vaginal oestrogens [9].

Low dose vaginal oestrogen replacement has minimal systemic absorption and therefore is unlikely to have an adverse effect on endometrial proliferation or the risk of endometrial hyperplasia compared with systemic therapy. There is therefore no need for concomitant progestogen therapy nor endometrial surveillance in asymptomatic women receiving low dose vaginal oestrogen therapy alone.

Non-hormonal options should be considered as first-line treatment in women with a history of breast cancer, particularly those receiving tamoxifen or aromatase inhibitors [10].

Women with breast cancer who do not respond to non-hormonal treatment may consider vaginal oestrogens. The pros and cons of off-label use of vaginal oestrogen therapy should be considered carefully and discussed with the woman's oncology team and menopause specialist. Women on aromatase inhibitors who wish to use vaginal oestrogen treatment should consider switching their adjuvant therapy to tamoxifen given that the mode of action of tamoxifen is through oestrogen receptor antagonism, while aromatase inhibitors exert their effect by lowering total oestrogen levels.

Musculoskeletal effects

The frequency of arthralgia and musculoskeletal pain symptoms appears to increase with age and is thought to be exacerbated by menopause. Oestrogen is known to play a regulatory role in cartilage metabolism, and menopause is associated with intervertebral disc thinning as well as osteoarthritic joint changes. Lifestyle recommendations such as weight optimisation, diet, and exercise can all help to improve symptoms as well as the use of HRT, particularly for arthralgia of the small joints and results from the WHI study showed significant improvement in joint aches with HRT compared to placebo [11].

Sarcopenia, which is defined as a progressive and generalised loss of muscle mass as well as muscle strength resulting in low physical performance, is also associated with declining oestrogen levels seen after menopause. Cochrane review data have shown that progressive resistance therapy 2–3 times a week is likely to be beneficial for the maintenance of muscle mass and balance [12].

The role of HRT in maintaining muscle strength is unclear. Greising et al. [13] showed in a meta-analysis that HRT users had 5% greater muscle strength compared to non-users. However, Javed et al. [14] conducted a more recent systematic review assessing the impact of HRT on lean body mass and found across 12 studies and 4474 postmenopausal women, there was no difference noted with HRT on muscle mass. In summary, although there appears to be a role for oestrogen in maintaining musculoskeletal function prior to menopause, the use of HRT has not been categorically shown to improve musculoskeletal function.

Cognition

Oestrogen receptors have been identified throughout the central and peripheral nervous system, and oestrogen has been shown to regulate both autonomic and cognitive functions. The hormonal changes resulting from menopause do appear to affect cognitive function in women. The symptoms that are reported can include forgetfulness, difficulty in concentrating, and a sensation of ‘brain fog’.

The relationship between cognition and HRT appears to largely depend on the woman's age and when HRT was commenced. Observational data suggest that HRT in women with premature ovarian insufficiency (POI), and early menopause appears to offer a protective effect on cognitive function and lowers the risk of dementia in this group of women [15].

Evidence from the WHI does not show any significant improvement or worsening in both memory and cognitive function for postmenopausal women over the age of 50 taking HRT [1]. However, subgroup analysis of women who initiated HRT at 65–79 years of age, in both oestrogen-alone and oestrogen/progestogen arms, suggested an increased risk of dementia. Statistical significance of increased risk was reached in the oestrogen and progestogen arm, however, not so for the increased risk seen in the oestrogen-alone arm.

Savolainen-Peltonen et al. (2019) published results pertaining to Alzheimer's disease risk with HRT from a nationwide case-control study in Finland. The study compared characteristics from 84,730 postmenopausal women diagnosed with Alzheimer's disease to 84,739 controls between 1999 and 2013. The study concluded that systemic HRT did appear to increase the risk of developing Alzheimer's disease with both oestrogen-only and combined oestrogen–progestogen and did not appear to be related to the type of progestogen used. Women under the age of 60 at the time of initiation of HRT had an increased risk of developing Alzheimer's with exposure of more than 10 years, while women over the age of 60 had an increased risk of developing Alzheimer's with any exposure [16].

Overall, the association between HRT and dementia risk remains unclear. Based on available evidence, women should be reassured that initiating HRT before the age of 60 is unlikely to increase the

risk of dementia or have a detrimental effect of cognitive function. HRT should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women. However, women with POI and early menopause are likely to gain potential cognitive advantage from HRT taken until the age of natural menopause, during the so-called the 'critical therapeutic window'. Rocca et al. (2014) referred to the concept of a cognitive window of opportunity and timing hypothesis [17]. In a review of the literature on the topic, the same group concluded that the initiation of hormone replacement in younger menopausal women is likely to lower the risk of cognitive impairment and dementia and recommended continuing it until the natural age of menopause.

Osteoporosis

Osteoporosis is a systemic skeletal disorder that causes reduced bone mass and micro-architectural deterioration of bone tissue, which in turn increases the risk of fragility fractures. The National Osteoporosis Guideline Group found that osteoporosis contributes to approximately 536,000 fractures each year in the UK [18]. Osteoporosis is more common in women than in men, and the hypo-oestrogenic state of menopause has been shown to accelerate bone density loss. This is compounded by the fact that women have a lower peak bone mass in comparison with men.

Osteoporosis treatment aims to reduce fracture risk. General lifestyle measures should be encouraged, such as maintaining a balanced diet, with adequate calcium and vitamin D intake; avoiding smoking and excessive alcohol intake; and partaking in regular exercise.

Oestrogen treatment as part of HRT for postmenopausal women is effective in preserving bone density and preventing osteoporosis in both the spine and hip as well as in reducing the risk of osteoporosis-related fractures.

As part of the NICE menopause guideline review, data from a total of 20 RCTs as well as from 21 comparative cohort studies were assessed. The evidence confirmed that women currently using HRT were significantly less likely to sustain any type of fracture compared to women not using HRT [4].

A systematic review and meta-analysis conducted by Zhu et al. (2016) with a total of 28 studies showed a reduction in total fractures with HRT (RR 0.74; 95% CI 0.69–0.80), hip fractures (RR 0.72; 95% CI 0.53–0.98) as well as for vertebral fractures (RR 0.63; 95% CI 0.44–0.91) [19].

Based on this evidence, most advisory bodies have recommended the use of HRT as a first-line therapeutic intervention for the prevention and treatment of osteoporosis for all women with POI, as well as in postmenopausal women under the age of 60, in particular those with menopausal symptoms.

The protective bone effect of HRT appears to be both dose and duration dependent, with a decline noted after discontinuation of treatment. Some studies have suggested; however, the use of HRT for a few years following menopause may provide a long-term effect that persists for many years even after stopping treatment [20].

Initiating or continuing HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended. Alternatives to HRT, such as the use of anti-resorptive agents including bisphosphonates, may be more appropriate of treatment for this cohort of women, with consideration given to seeking osteoporosis specialist advice for further assessment and discussion of management options.

Cardiovascular disease

Cardiovascular disease remains the leading cause of morbidity and mortality in women over the age of 50 years worldwide, and data from the British Heart Foundation have shown that approximately 24,000 women die each year in the UK from coronary heart disease.

There is consistent evidence to show that oestrogen has a protective effect against atherosclerotic changes, as well as being associated with a reduction in endothelial injury and lowering of total and LDL cholesterol levels, thus lowering plaque formation. Consequently, oestrogen therapy started around the time of menopause is likely to be cardioprotective, with a significant reduction in the incidence of cardiovascular disease, whether prescribed alone or combined with progestogen.

In the WHI RCT, early reports included combined outcomes for all age groups (50–79 years of age) and reported an increase in the risk of cardiovascular disease, with possible 'early harm' for women receiving combined oestrogen and progestogen (conjugated equine oestrogen 0.625 mg with medroxyprogesterone acetate 2.5 mg) [1].

However, all subsequent publications from the WHI including the long-term follow-up data from the WHI study group published in 2013 showed no evidence of a detrimental effect on coronary heart disease risk with combined oestrogen and progestogen replacement (coronary heart disease HR 1.09; 95% CI 0.96–1.24). For women starting oestrogen-alone below the age of 60, a decrease in the number of coronary events was noted [21]. More recently in 2017, the same study group found that with pooled long-term follow-up data, there was no adverse effect of taking HRT on cardiovascular mortality, either in the oestrogen-alone arm or in the combined progestogen arm (HR 1.00; 95% CI 0.92–1.08) [22].

Over the last decade, there has been increasing evidence to suggest a 'window of opportunity' in the primary prevention of cardiovascular disease when HRT is commenced before the age of 60.

The Danish Osteoporosis trial, which reported on data from over 1000 women aged 45–58, showed that for women commencing HRT within 10 years of menopause, there was a decline in the incidence of coronary heart disease, with a 50% reduction in a composite outcome measure which included heart failure, coronary events, and cardiovascular mortality as well as overall mortality [23].

The 'KEEPS' RCT reported on outcomes from 727 women randomised within less than 3 years of the last menstrual period. There were 3 arms in the study: 0.45 mg of oral conjugated equine oestrogen and 50 mg a day of transdermal oestradiol as well as a placebo group. For participants randomised to receiving active oestrogen, micronised progesterone was given for 12 days each month, and for participants in the placebo group, placebo capsules were given for the same duration [24].

Surrogate markers of cardiovascular function, namely coronary calcium scores and intima and media thickness as well as blood pressure, lipids, and insulin resistance parameters were assessed, and HRT appeared to exert a neutral effect on cardiovascular risk.

To evaluate the 'critical timing hypothesis' effect of HRT on cardiovascular risk, Hodis et al. (2016) conducted the 'Early versus Late Intervention Trial with Estradiol' (ELITE) [25]. A total of 643 postmenopausal women were randomised to receive placebo or oral oestrogen (1 mg oestradiol) plus micronised progesterone vaginal gel in women with a uterus. The results were stratified according to the duration from last menstrual period, with early defined as 6 years since menopause and late being 10 years or more since menopause. Carotid artery intima and media thickness were reported as the primary outcome, and HRT appeared to significantly lower the rate of atherosclerosis progression in the early initiation group, with a neutral effect (no benefit and no harm) in the late starting postmenopausal group.

Data from observational studies appear to also confirm RCT findings, with a 40% decrease in cardiovascular disease rates, as well as cardiovascular disease related mortality and all-cause mortality rates, in women who commenced HRT soon after menopause compared with non-users. This benefit was not seen in women starting HRT after the age of 60, and being consistent with the 'critical therapeutic window' theory.

A large observational study reported findings from a Finnish nationwide register between 1994 and 2009, consisting of 489,105 women [26]. A variety of HRT regimens were included oral and transdermal oestradiol, with approximately 1% of women receiving conjugated equine oestrogens combined with progestogens (primarily norethisterone acetate and medroxyprogesterone acetate) and 30,255 women receiving tibolone.

Compared to age-matched women, the rates of coronary heart disease-related death were reduced in HRT users within the first year of initiating treatment (IR 0.82; 95% CI 0.75–0.89). The risk reduction appeared to increase with time exposed to HRT up to 10 years of use. The rate of stroke death (IR 0.82; 95% CI 0.74–0.92) and of all-cause mortality (IR 0.88; 95% CI 0.85–0.91) was also reduced within the first year of HRT use. Overall, the study reported that in absolute terms, women, who used any regimen of HRT for 10 years or more, had 19 fewer coronary heart disease-related deaths and 7 fewer stroke-related deaths per 1000 women compared to controls.

Manson et al. (2019) published long-term follow-up data from the WHI study, which included 9939 women aged between 50 and 79, with 1129 of whom were aged 50–59 [27]. The results found a

significant reduction in all-cause mortality for women aged 50–59 receiving oestrogen therapy after a bilateral salpingo-oophrectomy compared to placebo (HR 0.68; 95% CI 0.48–0.96).

A Cochrane review published in 2015 assessed the effects of HRT in the context of prevention of cardiovascular disease in postmenopausal women [28]. Data from placebo-controlled RCTs were analysed, totalling 9088 women and showed a significant reduction in all-cause mortality, with 6 fewer deaths per 1000 women in those who started HRT within 10 years of their menopause, compared to placebo (RR 0.70; 95% CI 0.52–0.95). Placebo-controlled RCT data, totalling 8311 women also showed 8 fewer deaths per 1000 women from coronary heart disease (death from cardiovascular causes and non-fatal myocardial infarction) in those who started HRT within 10 years of their menopause, compared to placebo (RR 0.52; 95% CI 0.29–0.96). In women who started HRT more than 10 years after menopause, a neutral effect was noted with no difference in mortality or coronary heart disease compared to placebo or no treatment.

In summary, evidence from recent studies and Cochrane analysis suggests that HRT (oestrogen with or without progestogen) started before the age of 60 or within 10 years of menopause is associated with a reduction in atherosclerosis progression, coronary heart disease, and death from cardiovascular causes as well as all-cause mortality. Evidence from the Cochrane data analysis as well as the long-term follow-up data from the WHI appears to show no increase in cardiovascular events, cardiovascular mortality, or all-cause mortality in women who initiated HRT more than 10 years after menopause.

Stroke

Although the incidence of stroke in women under the age of 60 is low, it remains the second leading cause of mortality among females globally. Modifiable lifestyle factors that can contribute to the absolute risk of stroke, including obesity and smoking should be discussed with all postmenopausal women, as well as taking the opportunity to optimise health conditions such as hypertension, elevated cholesterol levels, and diabetes.

Results from the initial WHI study showed that across all age groups, oestrogen use, with or without progestogens, increased the risk of ischaemic stroke by about one-third (RR 1.31; 95% CI 1.02–1.68 and RR 1.37; 95% CI 1.09–1.73, respectively) [1].

A further study from the WHI group, with included 13 years' worth of follow-up data, also suggested an increased risk of stroke for the entire study group (age 50–79 years) in the combined oestrogen and progestogen arm (HR 1.16; 95% CI 1.00–1.35) as well as in the oestrogen-alone arm (HR 1.15, 95% CI 0.97–1.37). The increased risk was noted most significantly in women aged 60–69 in both arms [21].

A Cochrane review published in 2015 found an increased risk of stroke in women who commenced HRT within 10 years of the onset of menopause or before the age of 60 (RR 1.37; 95% CI 0.80–2.34); however, the increase was thought to be statistically insignificant [28]. For women who commenced HRT more than 10 years after menopause, there was a statistically significant increase in the risk of stroke (RR 1.21; 95% CI 1.06–1.38).

Large observational studies appear to show that the transdermal administration of oestradiol for HRT compared with oral administration is unlikely to increase the risk of stroke above that in non-users.

Renoux et al. (2010) showed that overall there was no increase in the risk of stroke with the current use of transdermal HRT compared to no use (RR 0.95; 95% CI 0.75–1.20) [29]. The risk of stroke was not increased with the use of low oestrogen dose patches (<50 μg a day) compared with no use (RR 0.81; 95% CI 0.62–1.05), whereas the risk was increased with high dose patches (>50 μg a day), albeit with wider confidence intervals (RR 1.89; 95% CI 1.15–3.11).

In summary, oral oestrogen therapy has been shown to cause a small increase in the risk of stroke. Transdermal oestradiol is unlikely to increase the risk of stroke above a woman's own background risk and therefore should be the preferred route of administration for women at high risk as well those over the age of 60.

Additionally, the type of progestogens as part of combined HRT may also influence stroke risk, and therefore micronised progesterone and dihydrogesterone should be considered as they are associated with a lower risk of stroke compared to other progestogens based on observational study data.

Venous thromboembolism

The risk of venous thromboembolism (VTE) is an important factor in determining the risk–benefit calculation when considering starting HRT. A woman's preliminary risk of acquiring a VTE is determined by the presence of co-existing risk factors such as age, obesity, personal or family history of VTE, the presence of hereditary thrombophilia's and immobility.

Overall the estimation of risk of VTE with HRT is determined by the presence or absence of the aforementioned factors, i.e., pre-existing intrinsic risk as well the characteristics of the HRT selected for use.

There is substantial evidence that the route of administration of HRT is the single most important determinant of VTE risk. The association of oral HRT and VTE is well established, and in women aged 50–59 years old, there is estimated to be an additional 2 thromboembolic events per 1000 women with 5 years of unopposed oestrogen [30]. This increased risk appears to be highest within the first year of intake of HRT containing oral oestrogen and this effect is no longer noted once HRT is stopped. Conversely, both meta-analyses and large observational data have shown no additional VTE risk above baseline associated with HRT containing transdermal oestradiol [31]. This is likely to be due to transdermal oestradiol avoiding the first-pass liver effect and its neutral effect on the coagulation cascade and the pro-inflammatory markers.

With oral HRT, the type and dose of oestrogen appear to affect VTE risk, with conjugated equine oestrogens being more prothrombotic than oestradiol. The type of progestogens also appears to impact VTE risk, with micronised progesterone and dihydrogesterone being more favourable to other types of synthetic progestogens.

A meta-analysis conducted by Scarabin (2018) compared the risk of VTE with HRT preparations containing oral versus that with transdermal oestradiol use [32]. The meta-analysis included a total of 26,471 VTE cases from 7 population-based observational studies. The data showed that for women taking oestrogen-only oral HRT there was an increased risk of VTE compared to non-users (RR 1.48; 95% CI 1.39–1.58). When comparing women taking transdermal oestradiol to non-users, there was no additional risk of VTE (RR 0.97; 95% CI 0.87–1.09).

For women requiring progestogens as part of combined HRT, there was no additional risk of VTE seen with transdermal oestradiol and micronised progesterone compared to non-users (RR 0.93; 95% CI 0.65–1.33). However, with norpregnane derivatives, there appeared to be an increased VTE risk compared to non-users (RR 2.42; 95% CI 1.84–3.18). An even greater risk of VTE was also seen with medroxyprogesterone acetate (RR 2.77; 95% CI 2.33–3.30).

In summary, HRT preparations containing transdermal oestradiol, with micronised progesterone or dihydrogesterone are unlikely to increase VTE risk above that in non-users. This is particularly pertinent for women with pre-existing risk factors for VTE, such as obesity, a personal history of VTE and/or a family history of VTE. Oral oestrogens should be avoided in postmenopausal women with a high baseline VTE risk.

For women with intrinsic risk factors, including women with a personal history of VTE, consideration should be given to review with a hematologist prior to commencing HRT.

Premature ovarian insufficiency

POI describes a condition characterised by an early cessation of menses, sex steroid deficiency, and elevated gonadotropins, occurring in women under the age of 40. Other terms used to describe POI have include premature ovarian failure and premature menopause.

Women with POI are at increased risk of osteoporosis, cardiovascular disease, and cognitive impairment and hormone replacement are likely to lower the long-term risk of cardiovascular disease in women with POI, prevent osteoporosis, and have a beneficial effect on cognitive function.

The aim of HRT for POI is to maintain oestrogen activity equivalent to age-matched ovarian function. Oestrogen activity should be maintained at physiological levels and should be advised to be taken until at least the estimated age of natural menopause, typically 51 years of age.

HRT and the combined contraceptive pill (COC) which containing ethinyl oestradiol can be used as oestrogen replacement. However, evidence suggests that HRT may be more beneficial in the

maintenance of bone health as well as cardiovascular health compared to COC with RCT data from several small studies showing improved bone density as well as more favourable blood pressure profiles with HRT compared to COC [33].

Breast cancer

The lifetime risk of developing breast cancer in developed countries is 11% (one in nine), and every year more than two million women worldwide are diagnosed with breast cancer. In the UK, breast cancer is the leading cause of female cancers and is estimated to cause approximately 11,400 deaths each year. The potential increased risk of breast cancer associated with HRT remains one of the primary causes for concern and anxiety among patients and healthcare professionals.

The NICE guidelines published in 2015 concluded that HRT with oestrogen and progestogen can be associated with an increased risk of breast cancer [4]. The risk appeared to be related to treatment duration and reduces after cessation of HRT. The recommendations also concluded that oestrogen-alone HRT resulted in little or no increase in the risk of breast cancer.

Subsequently, a meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) in 2019 suggested that the risk of breast cancer with HRT is higher than previously quoted [34]. This is discussed in detail elsewhere in this edition. The findings from the CGHFBC meta-analysis remain in keeping with the NICE guidance 2015 analysis of the observational data on the risk of breast cancer and HRT. Subsequently, in 2020, long-term WHI data showed a significant decrease in the risk of the diagnosis of breast cancer with oestrogen-only HRT and a significant reduction in breast cancer mortality compared with placebo [35]. Women who took combined oestrogen and progestogen HRT had an increased risk of breast cancer compared to placebo, in keeping with NICE guidance conclusions, but showed no significant difference in breast cancer mortality compared with placebo.

Further, the E3N observational studies suggested a lower breast cancer risk in users of micronised progesterone and dihydrogesterone compared to users of other progestogens [36].

These findings should be explained to women when discussing the benefits and risks of HRT to help them make an informed choice. However, arbitrary limits should not be placed on the dose or duration of usage of HRT. The decision whether to take HRT, the dose of HRT used, and the duration of its use should be made on an individualised basis after discussing the benefits and risks with each patient. This should be considered in the context of the overall benefits obtained from using HRT including symptom control and improving quality of life as well as considering the bone and cardiovascular benefits associated with HRT use.

In women who have had a prophylactic oophorectomy as a result of being BRCA 1 and BRAC 2 gene mutation carriers, add-back HRT is suitable until the age of 50. With regards to women with a history of breast cancer, based on current evidence, systemic HRT should be avoided. Non-hormonal therapy options should be considered for women with breast cancer experiencing symptoms resulting from menopause.

In summary, current evidence would suggest that with oestrogen-only HRT, there appears to be little or no increased risk of breast cancer. The risk is not increased with vaginal oestrogen therapy, while with combined HRT, there appears to be duration-dependent increase in the risk of breast cancer. The use of micronised progesterone and dihydrogesterone in combined HRT appears to be associated with a lower risk of invasive breast cancer compared to other progestogens.

Routes and regimens for HRT

Oestrogens

There are several routes of administration by which oestrogen therapy can be delivered. Systemic oestrogen is available orally, transdermally (patch, gel, or spray), or as subcutaneous implants. Each route follows a different metabolic pathway and therefore confers advantages as well potentiating risks associated with intake.

It has been demonstrated that women receiving oral oestrogens have an alteration in parameters of thrombin generation compared to women not using HRT, while no such alterations are noted in

women receiving transdermal oestradiol [37]. Transdermal administration of oestradiol results in slow systemic release and avoids the first-pass liver effect associated with oral intake. Laboratory studies have shown that transdermal administration has a neutral effect on all parameters of thrombin generation with no adverse effect on liver pro-inflammatory markers and such is unlikely to increase the risk of venous and arterial thrombosis. This neutral effect on venous and arterial thrombosis has also now been demonstrated in large observational case-control studies as discussed in the earlier part of this article.

Transdermal oestradiol delivery systems currently used in practice include patch, gel, and spray preparations. Patches contain oestradiol dissolved onto an adhesive matrix. Depending on the matrix used, these patches have to be changed once or twice a week and serum concentrations reach a steady state often within a few days.

Local oestrogen therapy can be given using topical vaginal preparations. Low vaginal oestrogen delivery preparations include oestradiol tablets and low dose oestradiol releasing rings made from a silicone elastomer that require replacing every 3 months, while estriol comes in cream, pessaries, and gel preparations. All low-dose oestradiol preparations are considered equally effective, do not result in significant systemic absorption, and can be used long term.

When the vaginal mucosa is at its most atrophic, the greatest permeability occurs and as the mucosa matures permeability decreases. It is therefore common practice to start administering vaginal estrogens more frequently, initially often given daily for the first 2–3 weeks then continued in maintenance dose commonly given two to three times a week, which can be continued long term.

Progestogens

For women with an intact uterus, progestogens are recommended alongside systemic oestrogen therapy to confer endometrial protection, with the primary aim being to reduce the risk of endometrial hyperplasia and carcinoma. The endometrial protective effect exerted by progestogens is both dose and duration dependent per cycle.

A Cochrane review found that the increased risk of endometrial hyperplasia with unopposed oestrogen is also both dose and duration dependent with exposure between one and three years [38].

In perimenopausal women, a sequential combined regimen is generally advised that includes continuous oestrogen with 12–14 days of progestogen per cycle. The withdrawal of progestogens results in endometrial shedding and a subsequent withdrawal bleed.

Continuous combined HRT involves taking a sustained daily dose of progestogen with oestrogen, resulting in the downregulation of endometrial oestrogen receptors and this induces a thin atrophic endometrium. This combination is often referred to as 'bleed-free' HRT.

There is limited evidence to guide practice in relation to the role or need for progestogen replacement in women who have had a subtotal hysterectomy. It is common practice to consider sequential progestogens for up to 3 months, and if no bleeding is noted with this, to consider it unlikely that residual endometrium is present. At this stage, oestrogen-only therapy can be considered to be adequate. Ongoing progestogen intake should be considered if there are concerns that the remnant cervical stump may contain residual endometrial tissue in women who experience cyclical bleeding with sequential HRT.

Continuous combined HRT regimens should be considered in women following hysterectomy for severe endometriosis, as well as in patients who have undergone endometrial ablation.

Type of progestogens and side-effect profile

Progestogens are available as micronised progesterone or as synthetic progestogens (e.g., dihydrogesterone, medroxyprogesterone acetate, norethisterone, or levonorgestrel).

Synthetic progestogens (also referred to as progestins) are a diverse range of molecules, with varying affinities for the progesterone receptor (PR). In addition, progestogens have an additional affinity to other receptors including the glucocorticoid receptors (GR), androgen receptors, and mineralocorticoid receptors (MR). Agonist activity at these receptors can therefore result in side effects related to the activation of these receptors.

MR and GR receptor activation can lead to water retention and weight gain. HRT containing the progestogen drospirenone may be considered in progestogen-intolerant women as this may be associated with less progestogenic side effects due to its anti-mineralocorticoid activity.

Dihydrogesterone has been noted to have a more neutral metabolic and side-effect profile compared to other synthetic progestogens. These side-effect profiles should be considered when counselling women to decide the optimal type of progestin to use within their HRT regimen.

Evidence from large observational studies and case-control studies suggests that micronised progesterone and dydrogesterone may be associated with a lower risk of breast cancer and a lower risk of VTE and stroke compared to that noted with other progestogens [39,40].

Micronised progesterone is available as oral preparation and is also available as vaginal preparations (pessaries, gel, or capsules). The latter, however, is not licensed for use as HRT but can be used off-license to provide the progestogen component of HRT in women who experience progestogenic side effects with oral intake. Micronised progesterone has variable transdermal absorption and a systematic review concluded that transdermal administration of micronised progesterone is unlikely to provide sufficient endometrial protection and should not be used in this context.

Synthetic progestogens are available in oral preparations or within combined patch preparations containing norethisterone and levonorgestrel in combination with oestradiol. These provide sufficient endometrial protection and are widely used in this context.

The levonorgestrel-releasing intrauterine system (LNG-IUS) can be used for endometrial protection in HRT. The LNG-IUS contains 52 mg of LNG releases 20 μg/day and has a license for use within HRT for 4 years in several countries. However, clinical evidence has shown it provides sufficient progestogen replacement for up to 5 years and can therefore be used to provide progestogen replacement for up to 5 years within HRT.

Unscheduled bleeding on HRT

Unscheduled bleeding is common when commencing HRT. Persistent unscheduled bleeding beyond the first 4–6 months of starting HRT should be investigated with an ultrasound scan and endometrial biopsy if required. For women on sequential HRT regimens, the aim is to achieve a regular withdrawal bleed which is acceptable for the patient.

In order to alleviate ongoing unscheduled bleeding on continuous combined HRT, the dose of progestogen can be increased (e.g., increase micronised progesterone daily dose from 100 mg to 200 mg daily on a continuous basis).

For cyclical HRT regimes, if the withdrawal bleeds are heavy, prolonged, or irregular, the dose of progestogen can be increased (e.g., micronised progesterone 300 mg for 12 days a month instead of 200 mg) or the duration of cyclical intake increased to 21 days. Alternatively, a different progestogen preparation including the LNG-IUS may be considered.

After 1 or 2 years, women may choose to switch to a continuous combined regimen to stop as 'bleed-free' therapy, or to stay on the same regimen if they wish to have withdrawal bleeding and this is not bothersome. If breakthrough bleeding occurs following the switch to continuous combined HRT and does not settle after three to six months, consideration should be given to switching back to a sequential regimen for at least another year.

Compounded bioidentical hormones

The concept of bioidentical hormones refers to duplicates of hormones such as oestradiol, progesterone, dehydroepiandrosterone, and testosterone produced within the human ovary and adrenal. These preparations are produced from plant extracts and are similar to their biological equivalents in the body and have potential advantages over non-identical alternatives such as CEE, ethinyl oestradiol, or synthetic progestogens as discussed earlier in this article.

Bioidentical or body-identical forms of HRT (oestradiol, micronised progesterone, and testosterone) are available as regulated medicinal products approved by the regulatory authorities such as the MHRA/EMA/FDA, and these regulated bioidentical or body-identical HRT products should be differentiated from compounded bioidentical HRT preparations. A number of bioidentical hormonal

products are compounded by pharmacies and marketed as supplements/natural replacements. However, compounded bioidentical HRT products do not follow the same regulatory pathways applied to regulated prescribed medicine by the regulatory authorities such as the Medicines and Healthcare products Regulatory Agency [MHRA], European Medicines Agency [EMA], and the Food and Drug Administration [FDA].

There are concerns related to the purity, potency, and safety of these compounded bioidentical hormones. In addition, many such compounded products deliver progesterone transdermally in cream or gel preparations which have been shown to have variable absorption. This potentially can lead to fluctuating tissue availability and as a result may not provide sufficient endometrial protection.

Due to concerns described above, related to the use of unregulated compounded products, advisory bodies have recommended avoiding the use of unregulated compounded bioidentical hormones and that regulated bioidentical hormones should be prescribed instead.

Conclusion

In summary, HRT can be offered to peri- or early postmenopausal women to control moderate to severe menopausal symptoms, following discussion of benefits and risks of HRT intake with women. No arbitrary limits should be placed on the dose or duration of usage of HRT. This decision should be made on an individualised basis and should be considered in the context of the overall benefits and risks obtained from using HRT, including symptom management and improved quality of life and the cardiovascular and bone protective effects associated with HRT.

Practice points

- The long-term follow-up data from the WHI trial analyses as well as the literature review and recommendations included in the National Institute for Health and Care Excellence (NICE) guidelines should allay the fears around the risks involved with HRT intake.
- While there is currently less evidence for the widespread use of HRT for long-term chronic disease prevention, HRT is a proven effective treatment for the prevention and treatment of osteoporosis and the evidence shows HRT also reduces cardiovascular disease risk if started under the age of 60.
- An individualised approach to commencing and continuing HRT is recommended, as the benefit–risk balance may differ for each woman and for an individual woman over time. However, for most, commencing HRT before the age of 60 has a favourable benefit and risk profile and can result in significant improvement in quality of life.

Research agenda

- Research in the field of post-reproductive health should be maintained with further assessment of the benefit–risk profile with different progestogens used in HRT, the cognitive impact of menopause, and the effect of HRT, including transdermal oestradiol and micronised progesterone on cognitive function.

Declaration of competing interest

KV and HH declare no conflict of interests pertaining to this article.

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