The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women.

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Executive Summary

- All women should be able to access advice on how they can optimise their menopause transition and the years beyond.
- There should be a holistic and individualised approach in assessing and advising women, with particular reference to lifestyle advice and diet modification.

HRT for the management of menopausal symptoms

- HRT is the most commonly used treatment for managing menopausal symptoms and has been shown to be the most effective intervention in this context.
- 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.
- Arbitrary limits should not be placed on the duration of usage of HRT.

Long-term effects of HRT

- HRT should be considered the first-line therapeutic intervention for the prevention and treatment of osteoporosis in women with premature ovarian insufficiency (POI) and menopausal women below 60 years of age, particularly those with menopausal symptoms.
- Cochrane analysis 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.
- Cochrane data-analysis as well as the long-term follow up data from the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause.
- Women should be reassured that HRT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function in women initiating HRT before the age of 60.
- Current evidence suggests that estrogen alone HRT is associated with little or no change in the risk of breast cancer while combined HRT can be associated with an increased risk which appears duration dependent and may vary with the type of progestogen and route of estrogen administration used. However, this risk is low in both medical and statistical terms, particularly compared to other modifiable risk factors such as obesity and alcohol intake, and this should be taken in the context of the overall benefits obtained from using HRT. Vaginal estrogen has not been associated with an increased risk in breast cancer. Large observational trial data suggest that micronised progesterone and dydrogesterone are likely to be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens.
- A history of breast cancer should be considered a contraindication to systemic HRT.
- Epidemiological studies suggest that there may be a slight increase in the risk of developing serious and endometrioid ovarian cancer associated with HRT use.
- Unopposed estrogen therapy increases the incidence of endometrial cancer and this risk is largely avoided by the use of combined estrogen and progestogen therapy.
- Evidence suggests no increase in risk of recurrence with HRT in women with early stage endometrial cancer.
- Evidence suggests no adverse effect on survival rates with HRT in women with epithelial ovarian cancer.
- Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis or stroke above that in non-users and is associated with a lower risk compared with oral administration of estradiol. The transdermal route should therefore be considered as the first choice route of estradiol administration in women with risk factors.
- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.

POI

- Women with POI should be encouraged to use HRT at least until the average age of the menopause.

Routes and regimens

- Non-hysterectomised women require progestogen (administered for 12–14 days in a sequential regimen and daily in a continuous combined regimen) to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure.
- The potential benefits of bioidentical hormone therapy can be achieved using conventionally licensed products, without having to resort to unregulated compounded varieties from specialist pharmacies.

Progestogens/side effects

- Micronised progesterone has a more selective effect on progesterone receptors and results in less interaction with androgenic and mineral-corticoid receptors compared with other progestogens. Micronised progesterone can minimise the metabolic impact and side-effects associated with other progestogens.

Unscheduled bleeding on HRT

- Persistent unscheduled bleeding beyond 4-6 months from commencing HRT warrants investigation with ultrasound scan and / or endometrial biopsy.

Sexual function/androgens

- Testosterone therapy can be considered in women with distressing low sexual desire and tiredness particularly if HRT in the form of adequate levels of estrogen with or without progesterone has not been effective.

Alternatives to HRT

- Non-hormonal interventions may be of help in women who have a contra-indication to receiving HRT or who do not wish to take HRT.

Introduction

The menopause transition can have a considerable impact on many women. The majority of women will experience menopausal symptoms, and for a significant proportion troublesome symptoms may continue long-term. Hormone Replacement Therapy (HRT) is the most commonly used treatment for managing menopausal symptoms and has been shown to be the most effective intervention in this context.

This updated version of The British Menopause Society and Women's Health Concern recommendations on HRT evaluates the evidence on the role of HRT in managing menopausal symptoms as well as that of alternative therapies. It also reviews the effects of HRT on bone, cardiovascular and cognitive function. In addition, the document assesses the evidence on the risks associated with HRT including venous thromboembolism, stroke and cancer and discusses the publication from the Collaborative Group on Hormonal Factors in Breast Cancer published in the Lancet in 2019.

The document also reviews progestogen regimens and the management of unscheduled bleeding on HRT and concludes with a summary of recommendations.

The BMS key recommendation is that all women should be able to access advice on how they can optimise their menopause transition and the years beyond. There should be a holistic and individualised approach in assessing and advising women, with particular reference to lifestyle advice and diet modification. This should be an opportunity to discuss the advantages and disadvantages of their management options including HRT and complementary therapies.

An extensive reference section and links to useful websites provide an opportunity to access evidence-based information in each key area.

HRT for the management of menopausal symptoms

Vasomotor symptoms

Vasomotor symptoms (VMS) which include hot flushes and night sweats are the commonest symptom affecting menopausal women and it is estimated that approximately 75% of menopausal women experience VMS with approximately a third of this group being severely affected. These symptoms often start in the one or two years before the menopause, the median duration of these symptoms is over 7 years and may persist for up to 15 years in 20% of women.

VMS can disturb sleep and can aggravate symptoms of tiredness, depressed mood and anxiety. They may also be associated with palpitations (racing or fluttering heartbeat).

32 randomised controlled trials (RCTs) have reported on interventions for the management of vasomotor symptoms in menopausal women and demonstrated a beneficial effect for HRT. A Cochrane systematic review summarised the results of 24 placebo-controlled randomised trials and showed a clear beneficial effect with estrogen replacement compared to placebo. Estrogen replacement remains the most effective treatment for VMS.

A network meta-analysis model undertaken by the NICE menopause guideline group reported on the cost-effectiveness of 5 years use of HRT. The analysis showed that both transdermal and oral HRT were effective treatment options, but suggested that transdermal HRT was more effective for relieving vasomotor symptoms as well as being more cost-effective as an intervention compared with oral HRT. Transdermal HRT was noted to be more cost-effective as vasomotor symptom severity increased and it had lower discontinuation rates.

The optimum dose and duration of HRT treatment should be decided according to the severity of a woman's symptoms as well as her response to therapy and arbitrary limits should not be placed on the dose or duration of usage of HRT.

Mood

Women are at increased risk of mood changes including depression and anxiety. Women with a history of premenstrual syndrome and postnatal depression are at particular risk.

Observational data suggest that the short-term use of HRT may improve mood and depressive symptoms during the menopausal transition and in the early menopause. In addition, there is evidence that cognitive behavioural therapy (CBT) may be beneficial for the management of low mood and anxiety.

Women with perimenopausal depression are often intolerant to progestogens, with many women reporting mood changes during the progestogenic component of combined sequential HRT. Micronised progesterone is associated with fewer side effects than the more androgenic progestogens which are best avoided in such women.

Women with severe depression and those who do not respond to HRT may benefit from psychiatric evaluation.

Sexual function

Estrogen replacement, systemic or topical, may improve sexual function. Systemic estrogen replacement can improve sexual desire and libido. In addition, topical vaginal estrogen replacement can improve dyspareunia secondary to vaginal atrophy, through its proliferative affect on the vulval and vaginal epithelium.

The administration of systemic testosterone has been shown to result in significant improvement in sexual function, including sexual desire and orgasm.

The recent Global consensus position statement on the use of testosterone therapy for women has confirmed the value of testosterone therapy for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women with no significant adverse events when testosterone levels are maintained within female physiological range. 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.

The indications for androgen replacement therapy, and its advantages and disadvantages are discussed in more detail elsewhere in this document.

Vulvovaginal atrophy / Genitourinary syndrome of the menopause

Traditionally referred to as vulvovaginal atrophy (VVA), the North American Menopause Society and International Society for the Study of Women's Sexual Health have proposed the new terminology "Genitourinary syndrome of the menopause" to indicate that both the urinary and genital areas can be affected by this condition (Portman et al. 2014), This terminology has not yet been widely adopted, except in North America.

Symptoms related to urogenital atrophy have been reported to be experienced by approximately 50% of postmenopausal women. Topical vaginal estrogen treatment has been shown to be effective in improving symptoms related to vaginal atrophy, such as vaginal dryness and superficial dyspareunia.

Estrogen also has a proliferative effect on bladder and urethral epithelium and may help relieve symptoms of urinary frequency, urgency and possibly reduce the incidence of recurrent urinary tract infections in women with urogenital atrophy.

Low-dose vaginal estrogen preparations can be used in symptomatic women and continued for as long as required. All topical estrogen preparations have been shown to be effective in this context.

There is no requirement to combine vaginal estrogens with systemic progestogen treatment for endometrial protection, as low-dose vaginal estrogen preparations do not result in significant systemic absorption or endometrial hyperplasia.

Intravaginal Dehydroepiandrosterone (DHEA) has been reported to be effective in the alleviation of symptoms of vulvovaginal atrophy.

In vivo studies have shown that vaginal DHEA increased vaginal epithelial mucin production, improved vaginal wall muscular thickness, and collagen fibre compactness. A placebo controlled double-blind RCT assessed vaginal DHEA 0.5% administered daily in a dose of 6.5 mg for 12 weeks and showed DHEA to be associated with significant improvement in vaginal epithelial thickness, secretions and vaginal pH.

Studies have shown no significant change in serum estradiol, DHEA, testosterone levels with vaginal DHEA 0.5% intake of 6.5 mg and intake for up to 52 weeks was noted to be associated with endometrial atrophy or inactive endometrium on endometrial biopsy samples.

Head to head comparisons of safety and efficacy of vaginal DHEA to topical vaginal estrogens are not available and further research is required to assess this.

Ospemifene is a selective estrogen receptor modulator (SERM) is an effective treatment for the symptoms of VVA and has recently been licensed in the UK. It is an oral preparation which may be a personal preference for some and may offer an alternative option to many older women who may find using a vaginal preparation technically difficult.

A meta-analysis included 6 RCTs with a total of 2086 patients. The analysis showed that Ospemifene in a dose of 60mg is associated with significant improvement in different vaginal morphological and physiological features. The review concluded that Ospemifene appears to be an effective treatment for vaginal dryness and dyspareunia associated with postmenopausal VVA.

Musculoskeletal effects

The prevalence of musculoskeletal pain and arthralgia in women increases with age and is aggravated by the menopause. Estrogen deficiency after the menopause has been reported to have a negative effect on connective tissue metabolism in joints, bone matrix, skin, intervertebral discs and elsewhere in the body.

Menopausal symptoms may include arthralgia, particularly of the small joints, and this may improve with HRT.

Lifestyle modifications such as optimising weight, diet and exercise are effective first line interventions for the management of arthralgia and osteoarthritis. RCT data including WHI have shown significant improvement in joint aches with HRT ($P<0.001$) showing a beneficial role for HRT in improving menopause related musculoskeletal symptoms.

The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as progressive and generalised loss of muscle mass and loss of muscle strength which may result in low physical performance.

Ageing and hormonal decline appear to have an adverse effect on muscle aging and regular physical activity appears to maintain muscle mass and balance. A Cochrane review of 121 randomised controlled trials concluded that progressive resistance therapy 2–3 times per week is the most beneficial intervention in this context.

Studies have suggested that estrogen may have a regulatory effect in mitigating the degree of muscular aging.

The evidence on the effect of HRT on improving muscle strength has been conflicting. A systematic review and meta-analysis by Greising et al. 2009 included data from 23 studies and approximately 10,000 post-menopausal women. The meta-analysis showed that postmenopausal women who received HRT had 5% greater muscle strength than those that did not receive HRT (P=0.003).

However, a more recent systematic review and meta-analysis by Javed et al. 2019 assessed the effect of HRT on lean body mass among postmenopausal women aged 50 years and older. The meta-analysis included 12 studies and 4474 postmenopausal women and did not show a significant beneficial or detrimental effect for HRT on muscle mass. The authors concluded that while muscle retention in aging women is of crucial importance, their findings suggest that interventions other than hormonal replacement need to be considered.

In summary, estrogen may benefit sarcopenia as it is associated with greater muscle power, regulation of muscle contraction, and favourable muscle composition.

Long-term effects of HRT

Osteoporosis

Osteoporosis is estimated to affect more than two million women in England and Wales. It is estimated that 1 in 2 women in the UK will suffer a fracture after the age of 50 and the International Osteoporosis Foundation reports that a 50 year old woman has a 2.8% risk of death related to hip fracture during her remaining lifetime. The National Osteoporosis Guideline Group (NOGG) estimates that 536,000 fractures are caused by osteoporosis in the UK every year and mortality rates with femur fractures are estimated to be 20% within the first year.

Advice should be given to menopausal women regarding lifestyle modification and bone health. This should include information on a balanced diet, adequate calcium and vitamin D intake, exercise, smoking cessation as well as avoidance of excessive alcohol intake.

The recommended daily intake of calcium for postmenopausal women is 1,000 mg and that for vitamin D is 1,000 IU a day. Supplements should be used where a need is identified, not routinely.

An assessment should be carried out to evaluate an individual woman's risk for developing osteoporosis and osteoporosis related fractures. Bone mineral density assessment is not a cost-effective screening tool for osteoporosis, and should be performed on a selective basis following an individual risk assessment. Fracture risk assessment can be carried out using the FRAX tool developed by the World Health Organisation to determine the need for treatment with bone preserving agents.

HRT has been shown to have a significant protective effect against osteoporosis and related fragility fractures and preventing osteoporosis in both spine and hip.

The NICE menopause guideline review assessed 20 RCTs that included sample sizes from 36 to 16,608 cases and 21 comparative cohort studies which included sample sizes from 157 to 170,852 cases. The evidence from RCTs in women in current users of HRT showed a significant reduction in the risk of any fracture compared with women not using HRT. The evidence from comparative cohort studies showed reduced risk of any and all fractures with current HRT use compared with non-use of HRT, whether used previously or never.

A systematic review and meta-analysis by Zhu et al. 2015 included a total of 28 studies with 33,426 participants and 2,516 fracture cases. Their meta-analysis noted a significant 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).

HRT should be considered the first-line therapeutic intervention for the prevention and treatment of osteoporosis in women with premature ovarian insufficiency (POI) and menopausal women below 60 years of age, particularly those with menopausal symptoms.

The bone-protective effect of estrogen is dose and duration related and the bone preserving effect of HRT declines after discontinuation of treatment.

However, recent studies have shown a bone-preserving effect even with relatively low doses of estrogen replacement. In addition, some studies have shown that the use of HRT for a few years around the menopause may provide a long-term protective effect many years after stopping HRT.

Cardiovascular disease

British Heart Foundation data show that approximately 24,000 women die from coronary heart disease each year in the UK and cardiovascular disease remains a leading cause for morbidity and mortality in women.

Over the last few decades observational studies have suggested that estrogen replacement was associated with a significant reduction in the incidence of

cardiovascular disease, whether prescribed alone or combined with progestogen.

In the Women's Health Initiative (WHI) randomised controlled trial, women received conjugated equine estrogens 0.625 mg alone or with medroxyprogesterone acetate 2.5 mg. The early reports from the WHI included all age groups in the study combined (50-79 years of age) and suggested an increase in the risk of cardiovascular disease and possible 'early harm' in women receiving combined estrogen and progestogen. However, the long-term follow up data, reported by the WHI study group in 2013 showed no evidence for a detrimental effect with combined estrogen and progestogen replacement (coronary heart disease HR 1.09; 95% CI 0.96-1.24). In women initiating HRT below 60 years of age, estrogen alone resulted in a significant decrease in coronary events.

A further long-term follow up report from the WHI study published in 2017 found no effect of hormone therapy on cardiovascular mortality for pooled data including estrogen alone arm and combined estrogen progestogen arm (HR 1.00; 95% CI 0.92-1.08)

Within the last decade a number of randomised studies re-visited the cardiovascular 'timing hypothesis' which addressed the concept of a 'window of opportunity' for the primary prevention of cardiovascular disease when HRT is initiated before the age of 60.

Randomised controlled data of over 1,000 women aged 45-58 years from the Danish Osteoporosis trial have shown that hormone therapy commenced within 10 years of the menopause reduced the incidence of coronary heart disease by around 50% reducing a composite outcome that included heart failure, coronary events and cardiovascular mortality as well as overall mortality.

The 'KEEPS' randomised controlled trial, included 727 participants who were less than three years from their last menstrual period. Women were randomised into three groups: 0.45 mg of oral conjugated equine estrogen, 50 micrograms a day of transdermal estradiol while women in the third group were given placebo. Women prescribed active estrogens received 200 mg of micronised progesterone for 12 days each month whereas women in the control group received placebo capsules.

The study reported a neutral impact on cardiovascular risk markers such as coronary calcium scores and intima media thickness with no negative effect on blood pressure, lipids and insulin resistance.

The 'Early versus Late Intervention Trial with Estradiol' (ELITE) by Hodis et al. 2016, reported on the cardiovascular effects of HRT in relation to the timing of initiation of treatment. A total of 643 postmenopausal women were randomised to receive either oral estrogen (1 mg estradiol) plus micronised progesterone vaginal gel for women with a uterus or placebo. Women were stratified according to the duration of time since their menopause. 'Early' was defined as less than 6 years since the menopause, while 'Late' was defined as 10 or more years since the menopause. The primary outcome assessed was atherosclerosis progression assessed by ultrasound measurement of carotid artery intima and media thickness. Estrogen treatment (with or without progesterone) resulted in a significantly lower rate of atherosclerosis progression in early postmenopausal women, but this effect was not noted in the late postmenopausal group.

Salpeter et al. 2009 reported a meta-analysis that included pooled data from 19 randomised trials of 16,000 women (mean age 55 years) followed up for 83,000 patient-years. The study showed a significant reduction in all-cause mortality with HRT intake compared to no treatment (RR 0.73; 95% CI 0.52-0.96). A similar conclusion was noted when data from 8 observational studies were added to the analysis (RR 0.72; 95% CI 0.62-0.82).

Mikkola et al. 2015, reported a large observational study that included data from 489,105 women from the Finnish nationwide reimbursement register and the Finnish national cause of death register that used HRT between 1994 and 2009. 3.3 million HRT exposure years were included. HRT regimens included oral and transdermal estradiol while approximately 1% of women received conjugated equine estrogens combined with progestogens (primarily norethisterone acetate and medroxyprogesterone acetate). A total of 30,255 women received Tibolone. The rate of coronary heart disease related deaths was reduced within the first year of HRT use compared to age-matched background population (IR 0.82; 95% CI 0.75-0.89) and this was positively related to HRT time exposure, with a risk reduction of 18-54% from 1 year 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. The risk reduction was positively related to HRT time exposure for both stroke (18% to 39%) and all-cause mortality (12-38%) from 1 year to 10 years of use. These reductions were noted in both women receiving estrogen alone and those receiving combined estrogen / progestogen preparations and were comparable for women who initiated HRT before the age of 60 years and those who started HRT after the age of 60 years. 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 1,000 women compared to controls.

Further, a recent long-term FU report from the WHI study by Manson et al. 2019 included a total sample size of 9,939 women aged 50-79 and of these 1,129 women were aged 50-59. The report showed a significant reduction in all-cause mortality (HR 0.68; 95% CI 0.48-0.96) in women aged 50-59 who received estrogen therapy after bilateral salpingo-oophorectomy compared to those who received placebo.

A Cochrane review published in 2015 assessed the effects of HRT in the context of prevention of cardiovascular disease in postmenopausal women. Placebo controlled RCTs with a total number of 9,088 women showed a significant reduction in all-cause mortality of 6 fewer deaths per 1,000 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 RCTs including a total of 8,311 women also showed 8 fewer deaths per 1,000 women from coronary heart disease (death from cardiovascular causes and non-fatal myocardial infarction) in those taking HRT compared to placebo (RR 0.52; 95% CI 0.29-0.96). On the other hand, a neutral effect was noted in women who started HRT more than 10 years after the menopause, with no difference in mortality (RR 1.06; 95% CI 0.95-1.38) or coronary heart disease (RR 1.07; 95% CI 0.96-1.20) compared to placebo or no treatment.

In summary, evidence from recent studies and Cochrane analysis suggests that HRT (estrogen with or without progestogen) 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.

Evidence from the Cochrane data-analysis as well as the long-term follow up data from the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause.

Cognition

Cognitive function in women appears to be affected by the hormonal changes of the menopause. Symptoms of forgetfulness, difficulty concentrating and brain fog are common at this time and observational data show an improvement in cognitive function with HRT started in early menopause. A late menopause may also confer some advantage.

The effect of HRT on the risk of dementia remains unclear, with studies reporting conflicting results.

Evidence from well-designed studies, including the WHI, shows no significant improvement or worsening in memory or cognitive function with HRT in older postmenopausal women. However, subgroup analysis reported an increase in the risk of dementia in women who initiated combined estrogen and progestogen at 65–79 years of age. This effect was also noted when both study groups were combined (estrogen alone and estrogen and progestogen arms). However, no statistically significant increase in risk was noted in the estrogen alone arm.

The Women's Health Initiative Memory Study (WHIMS), a study conducted on a subset of women recruited from the WHI trial, reported on 4532 women who commenced HRT over the age of 65 reported an increased risk of all-cause dementia in women taking conjugated equine estrogens 0.625 mg with medroxyprogesterone acetate 2.5 mg (HR 2.10; 95% CI 1.20-3.50), though not with conjugated equine estrogens alone (RR 1.50; 95% CI 0.80-2.70). However, women who commenced HRT at the age of 50-55 in the WHIMS-young study did not show any measurable differences in tests of cognitive function after an average of 7 years follow-up.

The KEEPS Cognitive and Affective Study included 693 women (220 women randomised to receive 0.45 mg/day oral conjugated equine estrogen with sequential micronised progesterone, 211 women randomised to receive 50 micrograms/day of transdermal estradiol with sequential micronised progesterone, and 262 women randomised to receive placebo. The study noted no improvement or worsening in cognitive outcomes during the 4 year intervention period of the study.

Savolainen-Peltonen et al. 2019 reported on the risk of Alzheimer's disease with HRT in a nationwide case-control study from Finland. The study included 84,739 postmenopausal Finnish women diagnosed with Alzheimer's disease compared to 84,739 controls between 1999 and 2013. The data were obtained from the Finnish national population register and controls were matched by age and hospital district.

The study concluded that systemic HRT increased the risk of developing Alzheimer's disease with both estrogen only and combined estrogen-progestogen and was not 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, whilst women over the age of 60 had an increased risk of developing Alzheimer's with any exposure.

The study findings do not demonstrate causality and there are a number of limitations to the study that need to be considered when interpreting the data. The authors report no statistical risk differences across age brackets. The distribution of cases was strongly skewed in terms of sample size towards the younger cases. Risk also appears to vary considerably between the different age brackets with 60-64 year olds appearing to have the highest risk. This would strongly suggest that there is a 'timing' effect and that the age of starting HRT may be crucial for the risk of developing or protecting against Alzheimer's disease. However, the skewed nature of the data might have overshadowed such an effect and limits the applicability of the findings.

Based on current evidence, women should be reassured that HRT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function in women initiating HRT before the age of 60. However, HRT should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women.

Cancer

Breast cancer

Breast cancer is the most commonly occurring female cancer in the UK and it is estimated that approximately 11,400 women die from breast cancer in the UK each year. Early diagnosis of breast cancer through screening and significant improvements in treatment have now resulted in the majority of women with breast cancer surviving their diagnosis.

Observational data from The Million Women Study (MWS) raised concerns over the long-term safety of HRT from the perspective of breast cancer.

Critique of the MWS has illustrated a number of key flaws in the study methodology and findings which limit the ability of the trial to establish a causal association between HRT and breast cancer.

The WHI estrogen and progestogen randomised controlled trial, reported a small increase in risk of breast cancer during the intervention phase after five years of usage of HRT of approximately one extra case per 1000 women per annum (HR 1.24; 95% CI 1.01-1.53), although this increase was no longer statistically significant when appropriate adjustment for confounding variables was made. In the early post-intervention phase (within 2.75 years from intervention, there was a sharp decrease in breast cancer risk in the combined arm and the risk became statistically insignificant (HR 1.23; 95% CI 0.90-1.70). However, during the late post-intervention phase (median 5.5 years post-intervention) a small increase in breast cancer risk was noted (HR 1.37; 95% CI 1.06-1.77).

In the WHI estrogen-alone trial, a small decrease in breast cancer risk was detected. The reduction in risk was not statistically significant during the intervention phase (HR 0.79; 95% CI 061-1.02). However, during the early post-intervention phase (within 2.75 years from intervention) the reduction in breast cancer risk in the estrogen alone arm became statistically significant (HR 0.55; 95% CI: 0.34-0.89). The risk reduction subsequently became neutral in the late (median 5.5 years post intervention) post-intervention phase (HR 1.17; 95% CI 0.73-1.87).

The literature review from the NICE 2015 guideline on the diagnosis and management of the menopause concluded that HRT with estrogen alone is associated with little or no change in the risk of breast cancer, while HRT with estrogen and progestogen can be associated with an increase in the risk of breast cancer. It also concluded that any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

A meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer published in the Lancet in August 2019 reported on the risk of breast cancer with HRT in relation to the type and timing of hormonal intake. The review covered the period January 1992 to January 2018 and included information from 58 studies of which 24 were prospective. Prospective follow-up identified 108,647 postmenopausal women who developed breast cancer of which 55,575 (51%) had used HRT. The meta-analysis did not collect information on breast cancer mortality.

The meta-analysis noted a duration-dependent risk of increased breast cancer diagnosis with both unopposed estrogen and combined HRT, risk with the latter being greater. In addition, the risk of breast cancer associated with continuous combined preparations was higher than sequential preparations, although the difference in absolute risk was small.

In absolute numbers, for women taking HRT for 5 years the increased risk reported in the meta-analysis was as

follows:

- For women taking continuous combined HRT for 5 years from the age of 50, the risk of developing breast cancer between the age of 50-69 goes up by 1 extra case in 50 over 20 years from a background risk of 3 out 50 women to 4 out of 50 women.
- For women taking sequential combined HRT for 5 years from the age of 50, the risk of developing breast cancer between the age of 50-69 goes up by 1 extra case in 70 over 20 years from a background risk of 4 out 70 women to 5 out of 70 women.
- For women taking estrogen only HRT for 5 years from the age of 50, the risk of developing breast cancer between the age of 50-69 goes up by 1 extra case in 200 over 20 years from a background risk of 13 out 200 women to 14 out of 200 women.

In past users of HRT, the risk of breast cancer was lower than in current users but the risk remained elevated more than 10 years after stopping. The increase, however, in absolute numbers was small.

The meta-analysis showed no dosage effect for estrogen on the risk of breast cancer with HRT and that vaginal estrogen exposure had no adverse impact on breast cancer risk with HRT.

There are a number of limitations that need to be taken into consideration when interpreting the findings from this meta-analysis. Over 40% of cases included in the meta-analysis were from the Million Women Study, which had significant methodological limitations. In addition, data from the placebo controlled WHI study were not included for comparison in the meta-analysis and only very small numbers of women on micronised progesterone were included. Data from the French E3N cohort study, which had demonstrated lower breast cancer risk in users of micronised progesterone compared to users of more androgenic progestogens, were not included in the meta-analysis.

The British Menopause Society is of the view that the meta-analysis provides important additional information on the risk of breast cancer with HRT. The findings, however, are consistent with NICE recommendations and should not be interpreted in isolation. These need to be discussed in the context of the overall benefits and risks associated with HRT to help women make an informed choice.

In December 2019, the WHI study group presented the long-term follow up data on the risk of breast cancer with HRT from the WHI study at an international breast cancer symposium. A total of 27,347 women were included of which 520 women breast cancer incidents were from the WHI estrogen only RCT, 1003 breast cancer incidents were from the WHI combined estrogen progestogen RCT. Women from the WHI estrogen only arm were followed up for 16.1 years and were reported to have a significant reduction in breast cancer incidence (HR 0.77; 95% CI 0.65-0.92) and mortality (44% reduction).

Women from the WHI combined estrogen progestogen arm were followed up for 18.3 years and were noted to have a significant increase in breast cancer incidence compared to controls (HR 1.29; 95% CI 1.14-1.47). The increased risk in the latter group persisted a decade after discontinuing HRT. No significant increase in mortality was noted with combined estrogen progestogen. **The full data from this report, however, were not available for analysis and the findings have not yet been published in a peer reviewed journal. This should be considered when interpreting the data.**

Analysis of the WHI data assessed the effect of being overweight or obese on the risk of breast cancer. Women who had a body mass index of over 35 had a significantly increased risk of invasive breast cancer compared with women of normal weight (HR 1.58; 95% CI 1.40-1.79). In addition, obesity was associated with an increase in estrogen receptor-positive and progesterone receptor-positive breast cancers (HR 1.86; 95% CI 1.60-2.17), an increase in advanced diseased (HR 2.12; 95% CI 1.67-2.69) and breast cancer mortality (HR 2.11; 95% CI 1.57-2.84) compared with women of normal body weight.

The 2019 meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer reported a modifying effect for obesity. The analysis noted an increase in the incidence of estrogen receptor positive breast cancer with increasing BMI in postmenopausal who had never used HRT. This effect was not noted in women who had been using HRT for some years. The review noted that in obese women, use of estrogen only HRT added little to their already elevated breast cancer risk related to the adiposity-associated estrogenic stimulation of their breast tissue.

However, lean and obese women had a similar increase in breast cancer risk by addition of a progestogen.

The authors concluded that obesity attenuated the absolute and the relative excess breast cancer risk associated with both unopposed and combined HRT.

Fornier et al. 2014, reported updated figures from the E3N Cohort, a large observational French study that included

3,678 invasive breast cancers between 1992 and 2008 among 78,353 women. HRT regimens that included estrogen and micronised progesterone or dydrogesterone were not associated with an increased risk of invasive breast cancer with short-term use up to 5 years (HR 1.11; 95% CI 0.89-1.38). Long-term use (more than 5 years) was associated with a slight increase in the risk of breast cancer (HR 1.31; 95% CI 1.15-1.48), but this risk was no longer statistically significant following discontinuation of HRT (HR 1.15; 95% CI 0.93-1.42).

HRT regimens that included estrogen and a progestogen other than micronised progesterone or dydrogesterone had a slightly elevated breast cancer risk with short-term use up to 5 years (HR 1.70; 95% CI 1.50-1.91) and with long-term use for more than 5 years (HR 2.02; 95% CI 1.81-2.26). A slight ongoing increase (HR 1.36; 95% CI 1.13-1.64) was also noted following discontinuation of HRT in this group.

In summary, results from the E3N French cohort study suggest:

1. Estrogens combined with micronised progesterone do not increase breast cancer risk for up to 5 years of use.
2. Estrogens with oral micronised progesterone for >5 years were associated with a small increased breast cancer risk.
3. Estrogens (either transdermal or oral) combined with synthetic progestins increase breast cancer risk at any duration of exposure with a duration dependent increase in risk.

Large observational trial data from the E3N Cohort and the Finnish Cancer Registry have reported no difference in the risk of invasive breast cancer with oral versus transdermal administration of estradiol. In addition, data from the Finnish Cancer Registry have suggested a similar risk of breast cancer with HRT regimens using the levonorgestrel intrauterine system to that noted with regimens using oral progestogens. The latter findings, as well as the effect of dose, duration of exposure and type of regimen require further evaluation in adequately powered prospective studies.

Women who are carriers of the BRCA1 and BRCA2 gene mutation who have undergone risk-reducing bilateral salpingo-oophorectomy, can receive add-back HRT and this has not been shown to diminish the risk-reducing benefit of BSO on subsequent risk of breast cancer diagnosis. A meta-analysis and recent systematic review on this, showed no increase in the risk of breast cancer in women with BRCA1 and BRCA2 mutations using HRT after risk-reducing bilateral salpingo-oophorectomy.

In summary, current evidence suggests that estrogen alone HRT is associated with little or no change in the risk of breast cancer while combined HRT can be associated with an increased risk which appears duration dependent and may vary with the type of progestogen used. However, this risk is low in both medical and statistical terms, particularly compared to other modifiable risk factors (e.g. obesity), and should be taken in the context of the overall benefits obtained from using HRT. Large observational trial data suggest that micronised progesterone and dydrogesterone are likely to be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens.

Endometrial cancer

Unopposed estrogen therapy increases the incidence of endometrial cancer and this risk is largely avoided by the use of combined estrogen and progestogen therapy.

Long-term use of sequential combined HRT for more than five years may be associated with a small increase in risk of endometrial cancer, with risk being inversely proportional to the number of days progestogen is given.

The WHI estrogen and progestogen study, reported a neutral effect on the risk of endometrial cancer with HRT compared to placebo during the intervention phase after five years of usage of HRT (HR 0.83; 95% CI 0.49-1.40). However, a significant reduction was noted with combined estrogen and progestogen intake compared to placebo in the post-intervention phase (HR 0.58; 95% CI 0.40-0.86) and with long-term cumulative follow-up (HR 0.67; 95% CI 0.49-0.91).

Ovarian cancer

Observational data have suggested an increased risk of ovarian cancer with HRT use.

The WHI estrogen and progestogen trial was the only randomised placebo controlled trial which studied the incidence of ovarian cancer in women taking combined equine estrogens plus medroxyprogesterone acetate and concluded that over long-term follow-up there was no evidence of increased risk (HR 1.24; 95% CI 0.83-1.87).

Data analysis from the Danish National Cancer Registry revealed a significant increase in the incidence of serious invasive ovarian tumours following eight years use of estrogen alone (IRR 1.7; 95% CI 1.4-2.1) and combined estrogen and progestogen therapy (IRR 1.6; 95% CI 1.4-1.9).

A meta-analysis by the Collaborative Group on Epidemiological Studies of Ovarian Cancer included individual data from 52 epidemiological studies, in which approximately half the postmenopausal women with ovarian cancer had used HRT. Ovarian cancer risk was significantly increased in current users receiving up to 5 years of HRT (RR 1.43; 95% CI 1.31-1.56). In past users, the risk decreased the longer the duration of time after discontinuation of HRT. However, the ongoing risk remained slightly elevated (HR 1.37; 95% CI 1.29-1.46). The risk did not differ significantly between users of estrogen alone and combined estrogen and progestogen preparations. In addition, the increased risk was only noted for serous and endometrioid cancers. The meta-analysis concluded that women who used HRT for 5 years starting approximately at the age of 50 years had an additional risk of developing ovarian cancer of approximately one extra case per 1000 users (which equates to one extra case per 5000 women per year) and a risk of having one extra death related to ovarian cancer per 1,700 users.

There are a number of limitations that need to be taken into consideration when interpreting the findings, including heterogeneity of the data, differences in study protocols and proportions of women lost to follow up in these studies.

More recently, Liu et al. 2019 reported a meta-analysis on the association of HRT with the risk of ovarian cancer by histological subtype. A total of 36 observational studies involving 4,229,061 participants were included in the meta-analysis and the review suggested a small increase in the risk of ovarian cancer with HRT (RR 1.29; 95% CI 1.19-1.40). Association differed between histological subtypes with an increased risk noted for serous (RR 1.50; 95% CI 1.35–1.68) and endometrioid (RR 1.48; 95% CI 1.13–1.94) cancers.

In summary, there may be a slight increase in the risk of developing serous and endometrioid ovarian cancer associated with HRT use. However, this risk is small in both medical and statistical terms and should be taken in the context of the overall benefits and risks balance for the individual woman.

Cervical cancer

While there is a known association between the combined oral contraceptive pill use and cervical cancer, there is no association between cervical cancer and HRT. The WHI study found no evidence for an increase in the risk of cervical cancer with HRT (HR 1.44; 95% CI 0.47-4.42).

The European Prospective Investigation into Cancer and Nutrition (EPIC) Study (2016) included a cohort of 308,036 women of which 261 women had invasive cervical cancer with a median follow-up 9 years and 804 women had CIN 3 / Carcinoma in situ. Ever use of HRT was associated with a statistically significant reduction in the risk of invasive cervical cancer (HR 0.50; 95% CI 0.40-0.80).

Colorectal cancer

Published data suggest a reduced risk of colorectal cancer with the use of oral combined HRT.

The WHI trial showed that the risk of colorectal cancer was reduced in the combined estrogen and progestogen arm (HR 0.62; 95% CI 0.43-0.89), though no effect was shown in the estrogen alone group (HR 1.15; 95% CI 0.81-1.64). The risk reduction of combined estrogen and progestogen reduced after stopping HRT over 13 years cumulative follow up (HR 0.80; 95% CI 0.63-1.01).

There are no data on transdermal HRT and the risk of colorectal cancer.

HRT after cancer

Breast cancer

The evidence on the risk of recurrence of breast cancer with the use of HRT is inconclusive as the number of breast cancer events in published studies is too small for definitive conclusions to be made. In addition, some of the analyses in the published literature were not based on a priori hypothesis.

A randomised, non-placebo-controlled Scandinavian RCT (HABITS - Holmberg et al., 2004, 2008) was terminated early after two years of follow-up as a significantly increased number of new breast cancer cases was noted in the HRT arm of the trial. The HABITS trial was initiated in 1997 and a total of 447 women were randomly assigned. Most women in the HRT arm received continuous combined or sequential estradiol and norethisterone.

The HABITS steering committee terminated the study in December 2003, when preliminary results based on a median follow-up of 2.1 years showed a significantly increased risk of breast cancer recurrence in the HRT arm of the trial (HR 3.5; 95% CI 1.5–7.4). A total of 442 women were followed up for a median of four years. Thirty-nine of 221 women in the HRT arm and 17/221 women in the control arm experienced a new breast cancer event (HR 2.4; 95% CI 1.3-4.2).

The authors concluded that after extended follow up, there

was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HRT.

The Stockholm trial was an open randomised trial that was initiated in 1997. A total of 188 women with a history of breast cancer were randomised to HRT, while 190 women were randomised to no HRT. The trial was prematurely stopped in 2003 when the HABITS trial findings, described above, were reported.

The Stockholm trial found no evidence for excess risk of breast cancer recurrence with HRT after a median follow-up of 4.1 years at the end date in January 2004 (HR 0.82, 95% CI 0.35-1.9). Long-term follow-up with a median of 10.8 years did not find evidence for any difference in new breast cancer events (60 in the HRT group vs. 48 in the control group (HR 1.3; 95% CI 0.9-1.9). However, there was a significantly higher number of contralateral breast cancers (14 cases) in the HRT group compared to the control group (4 cases) (HR 3.6; 95% CI 1.2-10.9). The authors concluded that it was uncertain whether these contralateral tumours should be regarded as a recurrence of the primary cancer or as a new primary malignancy. This finding is based on a very small number of events and there is no biological explanation for this discrepancy. It raises the issue to whether this outcome is due to the small number of breast cancer events.

There were a number of variations in the design of the HABITS and Stockholm trials that may account for the different outcomes noted. It has been suggested that the increased risk of recurrence in the HABITS trial might be attributed to greater progestogen exposure. However, the numbers for the different subgroups are too small to draw meaningful conclusions regarding the risk of recurrence associated with different progestogen regimens. In addition, the proportion of lymph node-positive patients was higher in the HABITS trial (26%) compared to the Stockholm trial (16%) and a greater percentage of women in the Stockholm trial were treated with adjuvant tamoxifen (52%) than in the HABITS trial (21%). However, subgroup analyses by the HABITS study group for use of tamoxifen and nodal status did not show a significant association, although the authors acknowledged that their subgroup analysis lacked sufficient power due to the small numbers included to confirm this conclusion.

The LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) was placebo-controlled double-blind randomised trial that assessed the safety and efficacy of tibolone in breast cancer patients. A total of 3098 women were included in the intention to treat analysis (1556 in the tibolone group and 1542 in the placebo group). The trial was ended prematurely in 2007, as interim analysis showed an overall increased risk of breast cancer recurrence in the tibolone group. After a median follow-up of 3.1 years, 237/1556 (15.2%) women in the tibolone arm had cancer recurrence, compared with 165/1542 (10.7%) in the placebo group (HR 1.40; 95% CI 1.14-1.70).

Based on current evidence, a history of breast cancer should be considered a contraindication to systemic HRT. Non-hormonal options should be considered for the management of menopausal symptoms in women with breast cancer.

Women with ongoing symptoms who fail to respond to non-hormonal management should be referred to discuss their options with their oncology team and menopause specialist to allow an individualised plan based on the woman's own circumstances.

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

Women with breast cancer who do not respond to non-hormonal treatment may consider vaginal estrogens. Off-label use of vaginal estrogen therapy can be considered in women with a history of hormone sensitive malignancies but the advantages and disadvantages of each case should be weighed up carefully and discussed with the woman's oncology team and menopause specialist.

Women on aromatase inhibitors who wish to use vaginal estrogen treatment should consider switching their adjuvant therapy to tamoxifen given that the mode of action of tamoxifen is through estrogen receptor antagonism while aromatase inhibitors exert their effect by lowering total estrogen levels.

Ospemifene is contraindicated in women undergoing active treatment for breast cancer. However, it may be used once treatment, including adjuvant therapy is complete although there is limited clinical evidence assessing this.

Additional research is needed to assess vaginal DHEA use in cancer survivors.

Endometrial cancer

Studies assessing the use of HRT following treatment for endometrial cancer have either shown no increased risk of recurrence or a reduced recurrence rate with an increased disease-free interval.

A meta-analysis by Shim et al. 2014 included one randomised trial and five observational studies. A total of 896 women with a history of endometrial cancer who

used HRT were included as well as 1079 non-users. The meta-analysis showed a decrease in recurrence in women taking HRT compared to the control group (OR 0.53; 95% CI 0.30-0.96).

HRT was initiated 1 to 60 months (on average 3-12 months) after surgery. Most of these studies have been on early stage disease and the findings may be different in advanced cancer where there may be microscopic metastatic deposits.

A Korean population study including 5667 women was conducted in 2019. This found no evidence for risk of endometrial cancer in women taking either estrogen alone (HR 0.78; 95% CI 0.31-1.96) or estrogen plus progestogen (HR 0.57; 0.21-1.57). However, although the study accounted for several important variables a key confounding variable, the stage of disease, could not be included in the analysis. This limits the reliability of the study's findings.

Endometrial sarcomas are estrogen sensitive and should be considered a contraindication to HRT.

Ovarian cancer

There is no evidence that estrogen therapy following treatment for ovarian cancer will adversely affect the prognosis.

Studies have either shown no difference in survival rates or an improvement in survival rates with the use of HRT in women with epithelial ovarian cancer.

Li et al. 2015 reported a systematic review and meta-analysis on postoperative HRT following epithelial ovarian cancer. The review included two RCTs and four cohort studies and included 419 women with epithelial ovarian cancer who used HRT and 1029 women with epithelial ovarian cancer who did not use HRT. The review concluded that postoperative HRT does not have a negative effect on overall survival (HR 0.68; 95% CI 0.54-0.86) and tumour recurrence (RR 0.83; 95% CI 0.64-1.07). The authors, however, acknowledged that there were methodological limitations in the included studies and recommended the need for well-designed and large-scale RCTs to further assess this.

Saeaib et al. 2020 reported a Cochrane review (Three RCTs, involving 350 women) on HRT after surgery for epithelial ovarian cancer. The review concluded that HRT may slightly improve overall survival in women who have undergone surgical treatment for epithelial ovarian cancer, but the quality of the evidence was low (HR 0.71; 95% CI 0.54-0.93).

There is no evidence assessing the effect of HRT on women with germ cell tumours. However, a small subset of germ cell tumours may be hormone sensitive and in this subset HRT should be avoided on theoretical grounds.

There are no data on the use of HRT following granulosa cell tumours though HRT should be avoided in this situation largely on theoretical grounds.

Ongoing hormone receptor studies on ovarian cancers may help predict the risk of recurrence.

Cervical cancer

HRT is not contraindicated after treatment for squamous cell carcinoma of the cervix or adenocarcinoma of the cervix.

Ploch 1987 reported on the use of HRT in cervical cancer survivors. 80 women with cervical cancer received HRT, while 40 women with cervical cancer were used as controls. Overall, no significant difference in recurrence rate or survival was noted between the two groups.

Vaginal and vulval cancer

Most vaginal and vulval cancers are squamous cell carcinomas and behave similarly to squamous cell carcinoma of the cervix and there is no evidence of an adverse effect with regard to recurrence of vulval disease. Thus, HRT would not be contraindicated and systemic and topical HRT can be used following vaginal and vulval carcinoma.

Venous thromboembolism (VTE)

The link between traditional oral HRT and venous thromboembolism (VTE) is well established: risk is increased 2-4 fold and is greatest in the first year after initiation. Additional factors might further increase the risk. This includes common risk factors such as older age and raised BMI or less common but significant factors such as thrombophilia or personal history of VTE.

The risk associated with HRT is determined by the interaction between the patient's intrinsic risk and the characteristics of the HRT. The single most important determinant of risk relating to HRT is route of administration. There is compelling evidence, from large observational studies and meta-analyses together with laboratory studies, that transdermal HRT does not increase the risk of VTE above that in non-users and is associated with a lower risk than oral estrogens. With

oral estrogens, the risk depends on the dose and type of estrogen, with conjugated equine estrogens more prothrombotic than estradiol. The type of progestogen significantly affects VTE risk with micronised progesterone and dydrogesterone conferring a lower risk compared to that with other synthetic progestogens.

Prior to commencing HRT, all women should be assessed for their risk of VTE. Routine thrombophilia testing is not necessary as this unlikely to alter the management plan.

A 2015 Cochrane meta-analysis included 19 RCTs and showed a significant increase in the risk of VTE in women who commenced HRT within 10 years of the onset of the menopause (RR 1.74; 95% CI 1.11-2.73) that increased in women who commenced HRT more than 10 years after the menopause (RR 1.96; 95% CI 1.37-2.80).

Scarabin 2018 reported a meta-analysis on the risk of VTE with oral versus transdermal estrogen and progestogens. The meta-analysis included 7 population-based observational studies (4 case-control and 3 cohort studies). No randomised trials were available for inclusion. A total of 26,471 VTE cases of which 735 were users of transdermal estrogen and 3,103 were users of oral estrogen were included as well as 22,633 non-users. Women taking oral estrogen-only preparations had an increased risk of VTE compared to women not on HRT (RR 1.48; 95% CI 1.39-1.58). However, women taking transdermal estradiol preparations had no increased risk compared to women not taking HRT (RR 0.97; 95% CI 0.87-1.09).

In women on combined HRT preparations, women taking transdermal estradiol with micronised progesterone did not have an increased risk above controls not taking HRT (RR 0.93; 95% CI 0.65-1.33). However, norpregnane derivatives (e.g. nomegestrol) were associated with an increased VTE risk compared to controls (RR 2.42; 95% CI 1.84-3.18). Medroxyprogesterone acetate, a pregnane derivative, was noted to have a higher risk of VTE compared to other synthetic progestogens (RR 2.77; 95% CI 2.33-3.30).

Vinogradova et al. 2019 reported two nested case-control studies that included 5,795 women with VTE on HRT and 21,670 controls on HRT. The study assessed the risk of VTE with different types of HRT preparations including different estrogens, delivery route and progestogen preparations. Estradiol was noted to have a lower risk of VTE compared to conjugated equine estrogen. For women taking combined HRT preparations, conjugated equine estrogen with medroxyprogesterone acetate had the highest risk, while estradiol with dydrogesterone had the lowest risk.

Transdermal preparations were not associated with an increased risk of VTE compared to women not taking HRT, and this finding was consistent for different regimens.

A neutral effect was noted with transdermal estradiol and this was noted with both low dose and high dose transdermal preparations.

Consideration should be given to prescribing transdermal estradiol instead of oral estradiol for menopausal women who are at increased risk of VTE, including those with raised body mass index. Consideration should also be given to using micronised progesterone or dydrogesterone in women at risk of VTE as these are unlikely to increase the risk of venous thrombosis compared with other progestogen preparations.

In the presence of known risk factors for VTE, including personal history of VTE or family history of VTE, the combination of transdermal estrogen and micronised progesterone offers a safe option that is unlikely to significantly increase VTE risk above the individual's intrinsic risk.

Discussion with a haematologist should be considered in postmenopausal women at particularly high risk for VTE who are being assessed for HRT.

Thromboprophylaxis in women on HRT who are admitted to hospital and women undergoing elective surgery

Hospitalisation for surgery or with medical illness must also prompt risk assessment for VTE. If women using HRT are admitted to hospital they should receive thromboprophylaxis as appropriate but do need to discontinue their HRT intake.

If elective surgery is planned, women require risk assessment. Current guidance suggests that HRT can be continued, whether transdermal or oral, as long as suitable thromboprophylaxis is given.

Stroke

Observational studies have yielded conflicting results regarding the risk of stroke with HRT.

The HERS study (the Heart and Estrogen progestogen Replacement Study) found no increase in the incidence of stroke with HRT.

The initial reports of the WHI study revealed an overall increased incidence of stroke in women using estrogen alone as well as those in the combined estrogen and progestogen arm.

The 13-year cumulative follow up data from the WHI study suggested an increased risk of stroke for the entire study group (age 50-79 years) in the combined estrogen and progestogen arm (HR 1.16; 95% CI 1.00-1.35) and (though with less certainty) in the estrogen alone arm (HR 1.15, 95% CI 0.97-1.37). This result appeared to be driven in particular by significantly increased risk in women aged 60-69 in both arms, as there were fewer stroke cases in other ages groups, meaning that risks were imprecisely estimated.

In addition, a 2015 Cochrane analysis showed no significant increase in the risk of stroke in women who commenced HRT within 10 years of the onset of the menopause or before the age of 60 (RR 1.37; 95% CI 0.80-2.34). The review, however, noted an increase in the risk of stroke in women who commenced HRT more than 10 years after the menopause (RR 1.21; 95% CI 1.06-1.38).

A recent systematic review and meta-regression analysis has shown a decrease in all-cause mortality when HRT is started before the age of 60. However, the risk of stroke was increased in all women taking HRT and this appeared to increase further with the age at which HRT was initiated.

On current evidence, HRT should not be recommended for the primary or secondary prevention of stroke.

Canonico et al. 2016 reported a dose-dependent increase in the risk of ischemic stroke risk with oral estrogen. The risk with low to medium estrogen dose of up to 1 mg/day showed OR 1.39; 95% CI 1.00-1.99, while that with higher estrogen doses of >1 mg/day showed OR 2.41; 95% CI 1.43–4.07.

Evidence from large observational studies has shown that transdermal administration of estradiol is unlikely to increase the risk of stroke above that in non-users and is associated with a lower risk of stroke compared with oral administration of estradiol. Renoux et al. 2010 reported no increase in the risk of stroke with current use of transdermal HRT compared to no use (RR 0.95; 95% CI 0.75-1.20). The risk of stroke was not increased with use of low estrogen dose patches (<50 micrograms 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 micrograms a day) but with wider confidence intervals (RR 1.89; 95 % CI 1.15-3.11).

Bagot et al. 2010 reported a laboratory study that assessed the changes in thrombin generation, a global coagulation assay and a marker of hypercoagulability, in women taking oral and transdermal HRT compared to that in women not taking HRT. All parameters of thrombin generation were altered in women using oral HRT compared with controls ($P<0.001$ for all comparisons). No such differences were found in women using transdermal HRT. Peak thrombin generation correlated with estrone and estradiol levels in women using oral HRT, but there was no significant correlation in peak thrombin generation with different serum estradiol or estrone concentrations with transdermal intake. These findings would suggest that transdermal estradiol has a neutral effect on thrombin generation and this neutral effect is maintained with different serum estradiol and estrone levels.

A similar neutral effect on the risk of stroke with transdermal estradiol was reported by Canonico et al. 2016 from a nested case-control French study. There was no evidence for a dose related effect on the risk of stroke with low dose transdermal estradiol [<50 micrograms a day] use (OR 0.69; 95% CI 0.37-1.28), intermediate dose estradiol [50 micrograms a day] (OR 0.79; 95% CI 0.40-1.58; or high dose estradiol [>50 micrograms a day] (OR 0.88; 95% CI 0.57-1.37).

Canonico et al. 2016, also reported in the same nested case-control study that the type of progestogen used within HRT may also have an effect on the risk of developing ischaemic stroke. The study included 3,144 hospitalised ischaemic stroke cases aged 51 to 62 years between 2009 and 2011 and women were matched for age and post-code to 12,158 controls.

There was no association of ischaemic stroke with use of progesterone (OR 0.78; 95% CI 0.49-1.26), pregnanes [e.g. medroxyprogesterone acetate, dydrogesterone and cyproterone acetate] (OR 1.00; 95% CI 0.60-1.67), and nortestosterones [e.g. norethisterone, levonorgestrel] (OR 1.26; 95% CI 0.62-2.58), while norpregnanes [e.g. nomegestrol] were associated with an increased risk of ischaemic stroke. (OR 2.25; 95% CI 1.05-4.81).

In summary, the literature assessing the risk of stroke with HRT shows the following:

-The risk of stroke is age related and overall the risk is low in women under the age of 60.

-Oral estradiol is likely to be associated with a small increase in the risk of stroke. This effect of is likely to be dose related and the lowest effective dose should therefore be prescribed.

-Transdermal estradiol is unlikely to increase the risk of stroke above the woman's own baseline risk. Consideration should therefore be given to administering estradiol transdermally in women with risk factors or those over the age of 60.

-The type of progestogen used in HRT may have an effect on the risk of stroke. Consideration should be given to using micronised progesterone or dydrogesterone with transdermal estradiol in women who are at increased risk.

Premature Ovarian Insufficiency (POI)

POI has been estimated to affect about 1% of women under the age of 40, 0.1% under 30 and 0.01% of women under the age of 20. However, as cure rates of cancers in young women continue to improve, it is likely that the incidence of iatrogenic prematurely menopausal women will rise.

HRT is strongly recommended in these young women to control menopausal symptoms, maintain sexual function as well as to minimise the risk of cardiovascular disease, osteoporosis, and possibly reduce the risk of cognitive impairment associated with POI.

The majority of women with POI (84-86%) will experience menopausal symptoms while approximately 40-50% will experience symptoms related to urogenital atrophy. Menopausal symptoms experienced by women with POI may vary in intensity and can be intermittent due to the fluctuation in ovarian activity.

Women with POI who do not experience menopausal symptoms would still be advised to consider hormone replacement for the prevention of the long-term sequelae of the condition.

Hormone replacement in POI simply replaces ovarian hormones that would normally be produced at this age.

The aim is to replace hormones as close to physiological levels as possible.

Hormone therapy should generally be continued at least until the estimated age of natural menopause (on average 51 years).

HRT is also important to preserve uterine function in women planning ovum donation.

5–10% of women with POI achieve a spontaneous pregnancy.

HRT and the combined contraceptive pill containing ethinyl estradiol would both be suitable options for hormone replacement. However, HRT may be more beneficial in improving bone health and cardiovascular risk compared to the combined oral contraceptive pill. Data from two small randomised trials have shown significantly greater improvement in bone density with HRT compared to that noted with the combined contraceptive pill as well as significantly lower mean systolic and diastolic blood pressure. Plasma angiotensin II and serum creatinine were reduced without alteration of plasma aldosterone concentrations with HRT compared with the combined contraceptive pill.

It is well recognised that young women with premature menopause will potentially be at an increased risk of osteoporosis, cardiovascular disease and cognitive impairment if adequate hormonal support is not used.

The WHI study findings do not apply to this young group as this study did not include women under the age of 50.

It is of paramount importance that the patients understand this in view of recent media reports on HRT.

There is an ongoing need to standardise terminology and to determine the causes and scale of the problem through a global registry (e.g. https://poiregistry.net). Good quality observational and randomised controlled trial data will facilitate the refinement of evidence-based guidelines (e.g. ESHRE Guideline on the management of premature ovarian insufficiency; 2015) which will optimise the management of POI.

POI and its health and fertility implications are discussed in further detail in separate consensus statement produced by the British Menopause Society and Women's Health Concern.

Early menopause

'Early menopause' refers to onset of the menopause between the age of 40 and up to 45 years of age. This group of women have similar long-term risks related to estrogen deficiency as those experienced by women with POI. Rocca et al. 2006 showed that mortality was

significantly increased in women who had bilateral oophorectomy before the age of 45 years compared to control women (HR 1·67; 95% CI: 1·16-2·40). Increased mortality was noted in women who had not received estrogen replacement up to the age of 45 years. In clinical practice, therefore, both groups (<40 and 40-45) are advised similarly regarding the bone and cardiovascular protective effects of sex steroid hormone replacement and should consider hormone replacement at least until the natural age of the menopause of 51 in the absence of a contra-indication.

The meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (2019) reported that the use of HRT in postmenopausal women younger than 50 increases risk of breast cancer diagnosis which contradicts previous evidence and advice to date. However, the control group in the meta-analysis was age-matched postmenopausal women rather than age-matched normally cycling women which would have provided a more accurate comparison (given that early menopause reduces breast cancer risk). In addition, the number of women in this subgroup was relatively small. These findings need to be taken in the context of the significant bone protective effects and cardiovascular benefits that HRT offers to younger postmenopausal women. Given the limitations above, the current recommendation that years of HRT exposure in women with POI should be counted from the age of natural menopause of 50 should stand.

Routes and regimens

Transdermal (gels, patches or spray) and subcutaneous (implants) administration of estradiol avoid the first pass effect through the liver and do not alter the coagulation cascade in the same way that oral estrogens do. Laboratory data have shown a neutral impact on thrombin generation, the coagulation cascade and pro-inflammatory markers with transdermal administration of estradiol. In addition, data from large observational studies have shown that transdermal administration of estradiol is unlikely to increase the risk of VTE or stroke above that of controls and has a lower risk than that which occurs with oral estradiol.

Non-hysterectomised women require progestogen (administered for 12–14 days in a sequential regimen and daily in a continuous combined regimen) to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure.

Intrauterine and vaginal routes of progestogen administration, such as the levonorgestrel releasing intrauterine system and progesterone gel and pessaries, provide adequate endometrial protection with reduced systemic side-effects.

The 52 mg levonorgestrel releasing intrauterine system provides adequate endometrial protection in women receiving estrogen therapy. Systemic side-effects are reduced though not completely eliminated. The impact on breast cancer risk remains unclear with preliminary data from the Finnish cancer registry showing no significant difference when compared to oral progestogens.

Continuous combined regimens avoid the need for regular withdrawal bleeds but may be associated with continuous low-grade progestogenic side effects. Unscheduled bleeding is higher with continuous combined HRT regimens compared to that with sequential regimens.

Ultra-low dose continuous combined estradiol and progestogen regimens (e.g. 0.5 mg estradiol in combination with dydrogesterone 2.5 mg) appear to maintain the benefits of higher dose regimens whilst allowing minimal use of progestogen to reduce side effects.

Low-dose vaginal estrogenic creams, rings, tablets and pessaries should be considered for women with symptoms of urogenital atrophy and can be used in conjunction with oral/transdermal HRT. It is estimated that up to 20% of women with do not obtain satisfactory control of their VVA symptoms when systemic HRT is used without topical vaginal estrogen treatment.

Long-term usage of topical vaginal estrogen treatment is commonly required as symptoms often return when treatment is discontinued and progestogenic opposition is not required as systemic absorption is minimal with low-dose estradiol and estriol vaginal preparations.

Conventionally regulated (non-compounded) bioidentical (rBHRT)' estradiol, progesterone and testosterone are produced from plant extracts and are similar to their biological equivalents in the body. They may have some advantages over non-identical varieties of HRT (e.g. ethinyl estradiol, synthetic progestogens) in terms of VTE and breast cancer risks. Recent case-controlled data indicate that the use of micronised progesterone is associated with a lower risk of VTE and breast cancer compared to that noted with other synthetic progestogens.

Compounded bioidentical hormone replacement therapies (cBHRT) are manufactured as creams, lozenges and vaginal preparations by 'Specialist Pharmacies' which have proliferated both physically and online in the UK and abroad. These cBHRT products:

• Do not follow the same regulatory pathway of evaluation by the MHRA as conventional pharmaceutical products

• Have not been through the rigorous process of drug development which conventional medicines and products such as conventionally regulated BHRT undergo

• Have not been scientifically evaluated in controlled randomised clinical trials for effectiveness and safety against placebo or conventional HRT.

The regulatory view is that compounding can only be justified when a medicine has to be created because the strength, concentration, or dosage form that is required for a specific patient is not commercially available.

Progestogens/side effects

Non hysterectomised women using estrogen therapy should use progestogen to minimise the risk of endometrial hyperplasia and carcinoma associated with unopposed estrogen exposure.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Study included 596 postmenopausal women who were randomised in equal numbers to the following five groups: (1) placebo; (2) conjugated equine estrogen, 0.625 mg/day; (3) conjugated equine estrogen 0.625 mg/day plus cyclic medroxyprogesterone acetate, 10

mg/day for 12 days/month; (4) conjugated equine estrogen, 0.625 mg/day plus continuous medroxyprogesterone acetate, 2.5 mg/day; or (5) conjugated equine estrogen, 0.625 mg/day plus cyclic micronised progesterone, 200 mg/day for 12 days/month. Unopposed estrogen was associated with an increased risk of endometrial hyperplasia compared with placebo ($p<0.001$). However, there was no significant difference in the risk of endometrial hyperplasia for any of the other groups compared with placebo.

A Cochrane review showed that unopposed estrogen replacement is associated with a significant increase in the risk of endometrial hyperplasia that is both dose and duration dependent with exposure between one and three years. Based on the evidence from studies included in the Cochrane analysis, the minimum required dose of progestogen given in a continuous combined regimen would be a minimum of 1 mg/day of norethisterone or 2.5 mg/day of medroxyprogesterone acetate. For low-dose sequential regimens, norethisterone 1 mg/day given for 10 days a month, oral micronised progesterone 200mg/day for 12 days a month, medroxyprogesterone acetate 10 mg/day for 10-14 days a month or dydrogesterone 10 mg/day for 14 days a month would be suitable options.

A systematic review by Stute et al. 2016, assessed the impact of micronised progesterone on the endometrium. Forty studies were included in the systematic review and it concluded that oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200 mg/day for up to 5 years. In addition, vaginal micronised progesterone may provide endometrial protection if applied sequentially for 10 days/month in a dose of 45 mg/day at 4% for up to 3–5 years. The systematic review concluded that transdermal micronised progesterone does not provide sufficient endometrial protection.

In the UK, vaginal micronised progesterone is available in 200 mg and 400 mg vaginal pessaries as well as a gel preparation that contains 90 mg of 8% micronised progesterone per application. The latter combinations are not licensed for use as HRT but can used off license to provide the progestogen component of HRT in women who experience progestogenic side-effects with oral intake.

If starting HRT de novo, a bleed-free regimen can be used from the outset if the last menstrual period was over a year ago.

If the last menstrual period occurred less than one year prior to starting HRT, a sequential combined regimen should be started, i.e. continuous estrogen with progestogen for 12-14 days per month.

After a minimum of one year of HRT, or one year after the last menstrual period, (two years in women with POI), women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined regimen which aims to give bleed-free HRT - this will also minimise the risk of endometrial hyperplasia.

Alternatively, women can be switched to the tissue selective agent tibolone.

One of the main reasons for reduced compliance with HRT is that of progestogen intolerance.

Progestogens protect the endometrium by inducing secretory transformation within the endometrial glandular epithelium. However, their use may result in a number of untoward side-effects.

Progestogenic side-effects may be reduced by using natural progesterone in the form of oral capsules. If ongoing side-effects with oral intake of progesterone, the capsules can be administered vaginally or alternatively switched to transvaginal progesterone pessaries or gels. In addition to the lower likelihood of side-effects, data from large observational studies have shown a lower risk of VTE and a lower risk of breast cancer with micronised progesterone compared to that noted with synthetic progestogens.

The 52 mg levonorgestrel intrauterine system minimises systemic progestogenic side-effects by direct release of progestogen into the endometrium. It has a four-year license in the UK for progestogenic opposition of estrogen hormone replacement therapy (five years in other countries). Studies have shown it to be effective and to offer sufficient endometrial protection up to 5 years within HRT regimens. As a result, it is common and safe practice to use the levonorgestrel intrauterine system for 5 years within HRT regimens (outwith its manufacturer's licence).

Androgenic side effects such as acne and hirsutism may be associated with the use of testosterone derived progestogens (such as norethisterone and levonorgestrel) due to stimulation of the androgen receptors.

Micronised progesterone has a more selective effect on progesterone receptors and results in less interaction with androgenic and mineral-corticoid receptors compared with other progestogens. Recent evidence suggests that HRT regimens containing micronised progesterone can minimise the metabolic impact and side-effects associated with other progestogens.

Dydrogesterone, a synthetic progestogen with a neutral metabolic profile and less adverse effect on breast tissue and thrombotic risk, can be used in combination with estrogen replacement. Dydrogesterone as a stand-alone preparation that can be used in combination with estrogen replacement was withdrawn from the UK market from March 2008 for commercial reasons. Dydrogesterone, however, continues to be marketed in the UK within combined HRT preparations.

Mood swings and PMS-like side effects result from adverse stimulation of the central nervous system progesterone receptors. The progestogen dose can be halved and duration of progestogen can be reduced to 7 to 10 days to minimise progestogenic side-effects. This may result in bleeding problems and may be associated with an increased risk of endometrial hyperplasia, so there should be a low threshold for ultrasound scanning and endometrial sampling if clinically indicated.

Symptoms of fluid retention result from the sodium retaining effect triggered by stimulation of the aldosterone receptors and the renin-aldosterone system.

Drospirenone, a spironolactone analogue, has anti-androgenic and anti-mineralocorticoid properties. It has been incorporated with low-dose estrogen in a continuous combined formulation offering an alternative in women with progestogen intolerance. This was discontinued for commercial reasons in the UK in 2018.

Unscheduled bleeding on HRT

Persistent unscheduled bleeding beyond 4-6 months from commencing HRT warrants investigation with ultrasound scan and / or endometrial biopsy.

For the majority of women with unscheduled bleeding on HRT, modifying progestogen intake would often control the bleeding especially in women who experience unscheduled bleeding in the first few months after commencing HRT.

Progestogen intake could be modified as follows:

For continuous combined HRT regimens the dose of progestogen could be increased (e.g. increase micronised progesterone daily dose from 100 mg to 200 mg daily on continuous basis). Those on continuous combined HRT regimens that contain a progestogen in a combined preparation or have the levonorgestrel intrauterine system, could have micronised progesterone / medroxyprogesterone acetate or norethisterone added to their HRT regimen. If they continue to experience ongoing unscheduled bleeding, the HRT regimen could be changed to a cyclical intake of progestogen.

For cyclical HRT regimens, the dose of progestogen could be increased (e.g. micronised progesterone 300 mg for 12 days a month instead of 200 mg) or increase duration of progestogen intake (can take progestogen for 14 days a month or for 21 days out of a 28-day HRT intake cycle).

Women who continue to have unscheduled bleeding beyond 6 months despite modifying their progestogen intake or where there is a concern about the clinical presentation or bleeding amount / pattern should have pelvic ultrasound scan assessment and endometrial biopsy or assessment of the endometrial cavity by hysteroscopy.

If breakthrough bleeding occurs following the switch to continuous combined HRT and does not settle after three to six months, then the woman can be switched back to a sequential regimen for at least another year.

The risk of endometrial cancer in women with unscheduled bleeding on HRT is significantly lower than that with postmenopausal bleeding in women not on HRT especially in women who had not been experiencing bleeding before commencing HRT and who are taking progestogen.

Sexual function/androgens

While there is an age related decline in sexual function including libido, arousal, orgasm and satisfaction, there is a significant decline around the time of the menopause.

Women with distressing low sexual desire and tiredness should be counselled that androgen supplementation is

an option particularly if HRT in the form of adequate levels of estrogen with or without progesterone has not been effective.

Assessment of serum androgen levels is unlikely to be beneficial in making the diagnosis of hormone dependent low sexual desire, as there is poor correlation between circulating androgen levels and clinical symptoms.

However, best practice as recommended by the Global Consensus Position Statement on the Use of Testosterone Therapy for Women is that testosterone levels should be checked to exclude high baseline levels and to prevent subsequent supraphysiological replacement.

Assessment of total testosterone levels (ideally by Mass Spectrometry techniques) should take into account sex hormone binding globulin levels. Free Androgen Index (FAI) = Total Testosterone x 100 / SHBG. Levels should be kept within the female physiological threshold (1.5-10%)

There are few licensed female androgenic options available globally even though there are accumulating data for efficacy and safety.

Testosterone implants and patches were withdrawn by pharmaceutical companies for commercial, not safety reasons.

Tibolone has a weak androgenic effect which can have a beneficial effect on mood and libido.

1% testosterone gel is available in 50 mg, 5 mL sachets and 2% testosterone gel in 60ml canisters for male use. Off-license prescribing by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 to mL/day, or 1.0 mL or 1 pump on alternate days both equating to a daily dose of 5mg/day. Alternate day administration, however, is likely to result in fluctuations in serum levels.

A 1% testosterone cream (0.5ml/day) with an indication for female use is manufactured in Australia and is only available privately at present in the UK.

Recent systematic reviews and meta-analyses by Achilli et al. 2017 and Islam et al. 2019 have shown that androgenic side effects and risks are minimal and reversible if testosterone levels are maintained within the female physiological range.

Some studies have shown benefits on the skeleton, cognition, well-being and the vagina, although these findings require further assessment.

Other options such as oral DHEA require further research to confirm their efficacy and safety. However, vaginal DHEA pessaries have recently been licensed for the treatment of vulvovaginal atrophy and may have some benefits for low libido. The latter, however, requires further evaluation in adequately powered randomised studies.

Lifestyle / Complementary and Alternative Therapies (CAMS) / Alternatives to HRT

Optimisation of diet and lifestyle advice should be incorporated into the routine management of all women in the menopause transition and beyond.

This should include advice on bone and cardiovascular health and information on adequate calcium and vitamin D intake, exercise, smoking cessation as well as avoidance of excessive alcohol intake.

Vaginal bioadhesive moisturisers are a more physiological way of replacing vaginal secretions than vaginal gels such as KY. They are hydrophilic and rehydrate vaginal tissues, providing a reasonable alternative to vaginal estrogen. Lubricants should have similar osmolality and pH to that of physiological vaginal secretions.

Pharmacological alternatives

A meta-analysis of 10 randomised controlled trials has shown a marginal benefit of clonidine over placebo in the control of menopausal vasomotor symptoms.

A significant amount of evidence exists for the efficacy of Selective serotonin reuptake inhibitors (SSRI's) such as fluoxetine and paroxetine in treating vasomotor symptoms.

The most convincing data are for the Serotonin and norepinephrine reuptake inhibitors (SNRI) (venlafaxine) in a dose of 37.5 mg bd in cancer survivors. However, the most common side effect, nausea, limits the usefulness of this agent. Fluoxetine and paroxetine should be avoided in tamoxifen users as they interfere with its metabolism and reduce its efficacy.

Low dose paroxetine was licensed in the USA by the FDA in 2013 for the treatment of vasomotor symptoms; systematic review and meta-analysis of moderate evidence supports its efficacy.

Small studies with the anti-epileptic drug Gabapentin have

shown effectiveness for hot flush reduction. A recent meta-analysis has confirmed superior efficacy compared to placebo for treating hot flushes. Its use is limited by side-effects such as drowsiness and somnolence, particularly at high doses. A stepwise increase in dosage by 300 mg per week up to a maximum of 1.2 g is advised to minimise side-effects.

An RCT, yet to be repeated, has demonstrated good efficacy for extended release oxybutyinin in the treatment of vasomotor symptoms. Side effects such as dry mouth were problematic in some patients as expected.

Preliminary studies of a novel treatment using Neurokinin 3 Receptor (NK3R) antagonism have been reported. This appears to be effective in the treatment of hot flushes and may be particularly helpful to women such as those with breast cancer in whom estrogen replacement is contraindicated.

Recent phase 2 clinical trials have demonstrated that neurokinin receptor antagonists are highly effective and well tolerated in alleviating vasomotor symptoms. A randomised, double-blind, placebo-controlled, phase 2a clinical trial in 87 postmenopausal women showed that NK3R 90 mg taken twice a day for 12 weeks of treatment significantly reduced moderate/severe VMS compared to placebo. A phase 2b, randomised, placebo-controlled, double-blind, dose-finding study, reported that all NK3R doses except the lowest dose (15 mg BD) resulted in significant reduction of moderate/severe VMS compared to placebo.

At the time of writing there are no licensed options available. Further assessment in larger phase 3 trials and for longer durations is needed before these agents become available as an option in standard clinical practice.

In summary, published literature shows a marginal benefit for non-hormonal interventions over placebo but they are likely to be less effective than HRT in controlling menopausal symptoms. However, non-hormonal interventions may be of help in women who have a contra-indication to receiving HRT or who do not wish to take HRT.

Phytoestrogens and Herbal Remedies

A recent large survey in the UK has shown that the prevalence of complementary and alternative therapy (CAM) usage including phytoestrogens in the UK is around 25% (1 in 4 women).

Data from some of the better researched phytoestrogen containing preparations appear to demonstrate some benefits, not only for symptom relief, but also on the skeleton and cardiovascular system.

A network meta-analysis undertaken by the NICE menopause guideline group showed that St John's wort and some isoflavone preparations may be effective for vasomotor symptoms but more research is required to confirm efficacy.

A model based meta-analysis of soy isoflavones showed a 25% reduction in hot flushes after elimination of the placebo effect.

There are as yet no hard data on major outcome measures such as coronary heart disease and fractures or long-term endometrial safety.

If a herbal treatment is chosen patients should look for the Traditional Herbal Remedy (THR) marking, validating strength and quality.

Acupuncture

A meta-analysis of the effects of acupuncture on frequency and severity of hot flushes, menopause-related symptoms, and quality of life in women in natural menopause showed a significant reduction in hot flushes and sweats. However, none of the studies included a sham control.

A double-blind, placebo (sham)-controlled randomised clinical trial determined the effects of acupuncture on menopausal hot flushes compared with sham therapy. The study found no evidence of a beneficial effect of acupuncture on vasomotor symptoms compared with sham therapy.

Further research is needed into the effects of acupuncture on vasomotor symptoms before it can be considered a more effective therapy than placebo.

Cognitive Behavioural Therapy (CBT)

CBT impacts on both VMS perception and reduction in stress and wellbeing, sleep problems and vasomotor symptomatology.

The efficacy and feasibility of a guided, internet-based CBT program in alleviating or reducing the severity of menopausal symptoms was evaluated in breast cancer survivors. 83% reported feeling more control over their symptoms after completing the program. Larger randomised trials are underway to assess the efficacy of the program.

A fact sheet on the Women's Health Concern website

provides guidance on CBT in a self-help format for women.

Laser for VVA

Treatment using CO2 and Erbium lasers have been used for the treatment of VVA. This is a novel treatment but emerging evidence suggests that this may have a place in the treatment of symptoms of VVA.

A double-blind placebo RCT by Cruz et al. 2018 included 45 participants and compared the efficacy of fractional CO2 vaginal laser treatment to local estriol therapy and the combination of both in the treatment of VVA in postmenopausal women over a 20 week period. All treatment arms resulted in improvement in vulvovaginal atrophy symptoms, vaginal health index scores and vaginal cytology analyses. The laser group showed significant worsening in the pain domain of the Female Sexual Function Index. These findings require further evaluation in larger randomised studies and over a longer duration of time.

A systematic review and meta-analysis by Pitsouni et al. 2017 assessed the efficacy of laser therapy for treating VVA. The meta-analysis included 14 studies and 542 participants with a follow up period between 1 and 18 months. All VVA symptoms including dryness / dyspareunia / itching / burning / dysuria / urgency / frequency and urinary frequency decreased significantly and consistently in all the included studies. The authors concluded that laser therapy appears to be a promising and safe non-pharmaceutical therapeutic option for managing VVA symptoms although the quality of the evidence assessed was low. These findings require further assessment in adequately powered RCTs.

Key points

- All women should be able to access advice on how they can optimise their menopause transition and the years beyond.

- There should be a holistic and individualised approach in assessing menopausal women, with particular reference to lifestyle advice, diet modification as well as discussion of the role 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.

- The HRT dosage, regimen and duration should be individualised, with annual evaluation of advantages and disadvantages.

- Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis or stroke above that in non-users and is associated with a lower risk compared with oral administration of estradiol. The transdermal route should therefore be considered as the first choice route of estradiol administration in women with risk factors.

- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.

- The potential benefits of bioidentical hormone therapy can be achieved using conventionally licensed products, without having to resort to unregulated compounded varieties from specialist pharmacies.

- Arbitrary limits should not be placed on the duration of usage of HRT; if symptoms persist, the benefits of hormone therapy usually outweigh the risks.

- HRT prescribed before the age of 60 has a favourable benefit / risk profile.

- HRT initiated before the age of 60 or within 10 years of the menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality.

- If HRT is to be used in women over 60 years of age, lower doses should be started, preferably with a transdermal route of estradiol administration. Evidence from the Cochrane data-analysis as well as that from the long-term follow up data of the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause.

- Women with POI should be encouraged to use HRT at least until the average age of the menopause.

- HRT and the combined contraceptive pill would both be suitable options for hormone replacement in women with POI. However, HRT may result in a more favourable improvement in bone density and cardiovascular markers compared with the combined contraceptive pill.

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Immediate Effects of HRT

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Further reading

- Post Reproductive Health – The Journal of the British Menopause Society, Eddie Morris and Heather Currie (eds), Sage Publications.
- Climacteric – The Journal of the International Menopause Society,Rod Baber (ed.), Taylor Francis .
- Maturitas – The Journal of the European Menopause Society, Margaret Rees (ed.), Elsevier Press.
- Management of the Menopause: The Handbook, Sixth edition. Published by the British Menopause Society 2017, London.
- Premature Menopause: A Multidisciplinary Approach Eds Singer D Hunter M WileyBlackwell London.
- Managing the Menopause: 21st Century solutions Eds Panay N, Briggs P, Kovacs G. Cambridge Medicine. (2nd Edition in Press)

Useful websites

- www.thebms.org.uk (British Menopause Society - see consensus statements)
- www.imsociety.org (International Menopause Society – see consensus statements)
- http://emas.obgyn.net/ European Menopause Society
- www.mhra.gov.uk (the medical and Healthcare Products Regulatory Agency)
- http://www.shef.ac.uk/FRAX/ (WHO osteoporosis fracture risk calculator)
- www.nos.org.uk (National Osteoporosis Society – professionals and patients)
- www.menopause.org (North American Menopause Society)
- http://www.ema.europa.eu/ema/ European Medicines Agency
- http://nccam.nih.gov/health/alerts/menopause/ National Centre for Complementary and Alternative Medicine Alternative therapies for managing menopausal symptoms.
- http://www.pcwhf.co.uk (useful information for woman's health in primary care).

- http://dietary-supplements.info.nih.gov The NIH Office of Dietary Supplements
- http://www.rcplondon.ac.uk/pubs/wp_osteo_ update.htm Royal College of Physicians Guidelines on Osteoporosis
- https://www.asa.org.uk/advice-online/health-bio-identical-hormone-replacement-therapy.html
- https://thebms.org.uk/publications/consensus-statements/non-hormonal-based-treatments-menopausal-symptoms/
- https://thebms.org.uk/publications/consensus-statements/bioidentical-hrt/
- https://www.womens-health-concern.org/wp-content/uploads/2017/02/WHC-FACTSHEET-01-CBT-WOMEN.pdf
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Information/support for women

- www.womens-health-concern.org
  (Women's Health Group – including 'ask the experts')
- www.menopausematters.co.uk

- www.managemymenopause.co.uk
  (personalised menopausal advice provided by experts)
- www.pms.org.uk (Premenstrual Syndrome website)
- theros.org.uk (Royal Osteoporosis Society – for both professionals and patients)
- www.daisynetwork.org.uk
  (Premature Menopause Society website)