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The British Menopause Society & Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women

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Introduction

The British Menopause Society (BMS) & Women's Health Concern 2016 recommendations on hormone replacement therapy (HRT) provide updated guidance based on recently published literature since the previous edition. The key data included in these updated recommendations include the cumulative long-term follow up outcomes from the Women's Health Initiative trial (WHI) that were published in 2013 and their practical significance. These recommendations also provide updated guidance relating to the changes in clinical practice post-WHI including the cardiovascular 'timing hypothesis' and 'window of opportunity', the role of transdermal administration of estradiol as well as that of micronised progesterone in this context.

Our 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 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

One of the main indications for prescribing HRT in postmenopausal women is the relief of vasomotor symptoms. The latter are estimated to occur in approximately 75% of postmenopausal women with approximately a third of this group being severely affected. The median duration of vasomotor symptoms is 7.4 years, and estrogen replacement remains the most effective treatment in this context.

Thirty-two 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.

A network meta-analysis model undertaken by the NICE menopause guideline group reported on the cost-effectiveness of five 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 duration of usage of HRT.

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Mood

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 may be beneficial for the management of low mood and anxiety.

Women with severe depression should be referred for mental health assessment.

Vulvovaginal atrophy/genitourinary syndrome of the menopause

Traditionally referred to as vulvovaginal atrophy, 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. Estrogen replacement has been shown to be effective in treating symptoms related to vaginal atrophy, such as vaginal dryness and superficial dyspareunia.

Estrogen also has a proliferative effect on the bladder and urethral epithelium particularly on the bladder trigone and the lower two-thirds of the urethra. It may help relieve symptoms of urinary frequency, urgency and reduce the risk 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.

However, there is little evidence to prove the safety of vaginal preparations beyond one year. Clinicians should therefore aim to use the lowest effective dose for symptom control and counsel women regarding this.

Non-hormonal moisturisers and lubricants can be used as an alternative but these are not as effective as estrogen therapy.

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.

Topical 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 after discussion with the woman's oncology team and menopause specialist.

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 vulvovaginal atrophy/genitourinary syndrome of the menopause, 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 indications for androgen replacement therapy and its advantages and disadvantages are discussed in more detail elsewhere in these recommendations.

Musculoskeletal effects

Estrogen deficiency after the menopause has been reported to have a negative effect on connective tissue metabolism in the bone matrix, skin, intervertebral discs and elsewhere in the body.

Observational data suggest that estrogen therapy has a protective effect against connective tissue loss and may possibly reverse this process in menopausal women receiving HRT.

Long-term effects of HRT

Osteoporosis

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 1000 mg and that for vitamin D is 1000 IU a day.

The Scientific Advisory Committee on Nutrition (SACN) reviewed the evidence on vitamin D and health and published its updated report on the topic in July 2016. The review identified that a significant proportion of the UK population had low vitamin D

concentrations. An estimated 22–24% of the 19–64-year-old age group had an annualised mean plasma vitamin D concentration below the 'population protective level' of 25 nmol/L. In addition, approximately 30–40% of the population had a plasma vitamin D concentration less than 25 nmol/L in winter compared to 2–13% in the summer.

The Committee report recommended a reference nutrient intake (RNI) of 10 μg (400 IU/day) of vitamin D per day, throughout the year, for everyone in the general population aged four years and older. This represents the average amount of vitamin D (from natural food sources, fortified foods or supplements) that is required to achieve a serum vitamin D concentration of 25 nmol/L or above during winter in 97.5% of the population.

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 Organization to determine the need for treatment with bone-preserving agents.

HRT is effective in preserving bone density and preventing osteoporosis in both spine and hip, as well as reducing the risk of osteoporosis-related fractures.

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.

However, initiating HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended.

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

Nonetheless, 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.

Bisphosphonates and other pharmacological agents can be used as an alternative to HRT to preserve bone density. Randomised trials have demonstrated that bisphosphonates significantly increase bone mineral density at both spine and hip. However, a theoretical concern exists regarding the possible over-suppression of bone turnover with long-term bisphosphonate treatment, which may result in a brittle skeleton and an increased risk of atypical fractures. Reports and case series have indicated a higher prevalence of fractures in the sub-trochanteric region of the femur and osteonecrosis of the jaw in patients on long-term treatment with bisphosphonates. The latter is generally associated with dental extraction. Consideration should therefore be given to a treatment discontinuation period of two years after five years of treatment with bisphosphonates.

Cardiovascular disease

Early observational studies suggested that HRT was associated with a significant reduction in the incidence of cardiovascular disease, whether estrogen was prescribed alone or combined with progestogen.

In the 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 detrimental effect with combined estrogen and progestogen replacement. This neutral cardiovascular effect was the same, regardless of the age women initiated combined HRT.

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 from the Danish Osteoporosis trial have shown that hormone therapy reduced the incidence of coronary heart disease by around 50% and reduced overall mortality if commenced within 10 years of the menopause in a study that included over 1000 women aged 45–58 years.

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 μg 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 six 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.

Mikkola et al. (2015) reported a large observational study that included data from 489,105 women from the Finnish National Registry that used HRT between 1994 and 2009. 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 risk of coronary heart disease related deaths was reduced by 18–54% and this was positively related to HRT time exposure. In addition, the risk of all-cause mortality was reduced by 12–38%, and this was also positively related to HRT time exposure. 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 per 1000 women compared to controls.

A Cochrane review published in 2015 assessed the effects of HRT in the context of prevention of cardiovascular disease in postmenopausal women. Those who started HRT within 10 years of their menopause had lower mortality (RR: 0.70; 95% CI: 0.52–0.95) and coronary heart disease, including death from cardiovascular causes and non-fatal myocardial infarction (RR: 0.52; 95% CI: 0.29–0.96) compared to placebo or no treatment. 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 or coronary heart disease 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

Observational data show an improvement in cognitive function when HRT is started in early menopause and a possible reduction in the long-term risk of Alzheimer's disease and all-cause dementia.

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 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 μg/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 four-year intervention period of the study.

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

Recent critique of the MWS has illustrated a number of key flaws which limit the ability of the trial to establish a causal association between HRT and breast cancer.

The WHI estrogen and progestogen study 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). 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: 0.61–1.02). 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).

No difference was noted in cancer deaths in the HRT arms of the study compared to placebo (HR for cancer deaths with combined estrogen and progestogen 1.07; 95% CI: 0.93–1.23 and HR for cancer deaths in the estrogen-alone arm 0.95; 95% CI: 0.81–1.13). In addition, no difference was noted in all-cause mortality in the HRT arms of the study compared to placebo (HR for all-cause mortality with combined estrogen and progestogen 0.99; 95% CI: 0.91–1.08 and HR for all-cause mortality in the estrogen-alone arm 0.99; 95% CI: 0.90–1.10) for the overall combined phases of the study (intervention and post-intervention phases).

Recent 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.

Fornier et al. (2014) reported updated figures from the E3N Cohort, a large observational French study that included 3678 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 five years (HR: 1.11; 95% CI: 0.89–1.38). Long-term use (more than five years) was associated with a small 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 five years (HR: 1.70; 95% CI: 1.50–1.91) and with long-term use for more than five 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.

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.

A recent prospective cohort study by Jones et al. (2016) reported on the risk of breast cancer with HRT. Women were recruited during the period 2003–2009. Information was collected from serial questionnaires, and the status of HRT use was updated through four years of follow-up. Among 39,183 women with documented menopausal age, 775 developed breast cancer. The use of estrogen-alone systemic HRT preparations was not associated with an increased risk of breast cancer compared to controls (HR: 1.00; 95% CI: 0.66–1.54). However, current use of combined estrogen and progestogen (median duration of current use 5.4 years) was associated with a significantly increased risk of breast cancer (HR based on 52 breast cancer cases: 2.74; 95% CI: 2.05–3.65 compared to non-users). This risk increased with longer duration of use (HR based on seven breast cancer cases who had combined estrogen and progestogen for 15+ years was 3.27; 95% CI: 1.53–6.99). The risk of breast cancer was not significantly increased in past users of HRT (HR one year after discontinuation of combined estrogen and progestogen: 1.61; 95% CI: 0.86–3.01). The authors also reported that the risk of breast cancer would have been underestimated if the information on HRT use was not updated after recruitment. They concluded that the lack of updating of HRT use status through follow-up is likely to result in underestimation of the risk of breast cancer associated with HRT.

Assessment was based on self-report questionnaires which would introduce the possibility of recall bias and the number of breast cancer cases particularly in the long-term follow-up groups was relatively small. In addition, the study did not report on the risk of breast cancer with different progestogen preparations.

These factors should be taken into consideration when interpreting the findings.

In summary, evidence from randomised trials shows that estrogen-alone HRT regimens are unlikely to increase the risk of invasive breast cancer. Combined estrogen and progestogen can be associated with a small increase in the risk of invasive breast cancer. However, this risk is low in both medical and statistical terms and should be taken in the context of the overall benefits obtained from using HRT. Large observational data suggest that micronised progesterone and dydrogesterone may be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens.

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

The WHI was the only randomised placebo-controlled trial which studied the incidence of ovarian cancer and HRT and concluded that there was no increased risk.

A recent data analysis from the Danish National Cancer Registry revealed a small but significant increase in the incidence of ovarian cancer following eight years use of estrogen-alone and combined estrogen and progestogen therapy.

A recent meta-analysis 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 five years of HRT (RR: 1.43; 95% CI: 1.31–1.56). In past users, the risk decreased the longer the duration of time was 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 five 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 1700 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.

In summary, there may be a slight increase in the risk of developing 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 – risks balance for the individual woman.

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.

Continuous combined regimens are associated with a significantly lower risk of endometrial cancer than an untreated population.

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 showed no significant increase in the risk of cervical cancer with HRT.

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, but there was a neutral effect in the estrogen-alone group.

There are no data on the effect of transdermal HRT and 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 showed no 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 showed no 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; $p = 0.013$). 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).

The conflicting results from these RCTs and their early termination make it difficult to draw firm conclusions regarding the possible risks of HRT in breast cancer survivors.

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.

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.

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.

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

Ovarian cancer. There is no evidence that estrogen therapy following the 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.

There is no evidence of an adverse effect of HRT on women with germ cell tumours.

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.

Vulval cancer. Systemic and topical estrogen can be used following vulval carcinoma. There is no evidence of an

adverse effect with regard to recurrence of vulval disease.

Venous thromboembolism

Individuals requiring HRT should be risk assessed and counselled regarding their venous thromboembolism (VTE) risk.

Routine thrombophilia testing is not required prior to commencing HRT but testing might be considered if there is a personal or family history of thrombosis.

Evidence from RCTs including the WHI as well as large observational studies has shown that oral estrogens increase the risk of VTE two- to four-fold, with the highest risk being in the first year of use.

VTE risk is further increased in those with a personal or family history of VTE, advanced age particularly beyond the age of 60, obesity and other risk factors such as surgery or hospitalisation.

Evidence from large observational studies and meta-analyses has shown that transdermal administration of estradiol is unlikely to increase the risk of VTE above that in non-users and is associated with a lower risk compared with oral administration of estradiol.

In addition, the risk of VTE may be affected by the type of progesterone used within HRT. There is increasing evidence that the risk is greater with certain progestogens such as norpregnane derivatives and medroxyprogesterone acetate. Evidence from observational studies suggests that micronised progesterone and pregnane derivatives such as dydrogesterone may be associated with a lower risk of VTE compared to other progestogens.

Menopausal women who are at increased risk of VTE including those with raised body mass index should be advised to take transdermal estradiol in preference to oral estradiol as the former is unlikely to increase their risk of venous thrombosis. In addition, consideration should be given to using micronised progesterone or dydrogesterone in women at risk of VTE as these may be associated with a lower risk of thrombosis compared to other progestogen preparations.

Women using HRT who are admitted to hospital require review of their therapy and should receive thromboprophylaxis as appropriate. Transdermal estradiol does not significantly alter the coagulation cascade. There is therefore no need to routinely discontinue transdermal HRT prior to elective surgery, especially when the surgery is minor and does not involve immobility. An individualised plan should be considered in discussion with the woman's surgical and anaesthetic teams.

Referral to a haematologist should be considered for postmenopausal women who are at high risk for developing VTE prior to commencing HRT.

Stroke

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

The Heart and Estrogen progestogen Replacement Study (HERS) 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 showed an increased risk of stroke for the entire study group (age: 50–79 years), in both the estrogen-alone and the combined estrogen and progestogen arms. However, the 13-year cumulative follow-up data from the WHI showed no significant increase in the risk of stroke in women aged 50–59 years with estrogen-alone treatment or with combined estrogen and progestogen.

In addition, Cochrane analysis showed no significant increase in the risk of stroke in women who commenced HRT before the age of 60 or within 10 years of the onset of the menopause. The review, however, noted an increase in the risk of stroke in women who commenced HRT more than 10 years after the menopause.

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

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.

A recent French nested case–control study reported by Canonico et al. (2016) suggested that the type of progesterone used within HRT may also have an effect on the risk of developing ischaemic stroke. The study included 3144 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 (OR: 1.00; 95% CI: 0.60–1.67), and nortestosterones (OR: 1.26; 95% CI: 0.62–2.58), while norpregnanes 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 background risk. Women with risk factors for stroke should therefore be advised to take transdermal estradiol in preference to oral estradiol.
- The type of progesterone used in HRT may have an effect on the risk of stroke. Observational data suggest that micronised progesterone or dydrogesterone may be associated with a lower risk of stroke compared to other progestogen preparations.

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.

Women with POI represent a different cohort to women who have natural menopause beyond the age of 50. The risks of hormone replacement including the risk of breast cancer quoted in the WHI and other studies on naturally menopausal women over the age of 50, do not apply to women with POI.

Hormone therapy should generally continue 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.

Women with POI can have intermittent ovarian activity and have a chance of natural conception. However, the likelihood of this is low and is estimated to be in the region of 5–10%.

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 markers compared to the combined oral contraceptive pill. Data from two recent 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.

'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 until the natural age of the menopause of 51 in the absence of a contraindication.

There is an urgent 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 POI; 2015) which will optimise the management of POI.

Routes and regimens

Transdermal (gels or patches) 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 replacement for 12–14 days a month to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure.

The uterine 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 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.

Ultralow dose continuous combined estradiol and progestogen regimens appear to maintain the benefits of higher dose regimens whilst allowing minimal use of progestogen to reduce side effects.

Unregulated compounded bioidentical hormones are not recommended due to lack of data for efficacy and safety.

Regulated non-compounded 'body-identical' 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).

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.

Indefinite usage is commonly required as symptoms often return when treatment is discontinued, and progestogenic opposition is not required as systemic absorption is minimal with estradiol and estriol vaginal preparations.

Off-label use of vaginal estrogen therapy can be considered in women with a history of hormone sensitive malignancy, but the advantages and disadvantages of each case should be weighed up carefully with close collaboration with the woman's oncology team and menopause specialist.

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. 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.

A double-blinded RCT by Kurman et al. (2000) was carried out to assess the lowest effective dose of norethisterone used in a continuous combined HRT regimen. A total of 1176 postmenopausal women aged 45 years or older were randomised to receive either 1 mg unopposed estradiol, or continuous combined regimens of 1 mg estradiol and norethisterone 0.1 mg, 0.25 mg, or 0.5 mg. Women were followed up over a 12-month period. Continuous combined regimens significantly reduced the incidence of endometrial hyperplasia compared with unopposed estradiol ($p < 0.001$). The incidence of endometrial hyperplasia associated with unopposed estradiol was 14.6%, whereas in all continuous combined groups, the rate of endometrial hyperplasia was less than 1%. Women who received norethisterone 0.1 mg had an incidence of endometrial hyperplasia of 0.8%, while those who received 0.25 mg and 0.5 mg had an incidence of endometrial hyperplasia of 0.4%.

Based on the evidence from the studies included, the authors of the Cochrane review recommended a minimum dose of medroxyprogesterone acetate of 1.5 mg/day in a continuous combined HRT regimen or norethisterone in a dose of 1 mg/day. The systematic review, however, concluded that norethisterone given in a dose of 0.1 mg or above provides adequate endometrial protection within a continuous combined HRT regimen.

For low-dose sequential regimens, norethisterone 1 mg/day given for 10 days, oral micronised progesterone 200 mg/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 recent 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 five 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% or every other day in a dose of 100 mg/day for up to 3–5 years. The systematic review concluded that transdermal micronised progesterone does not provide sufficient endometrial protection.

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. There may be some erratic bleeding to begin with, but on persistence with continuous combined regimens 90% of women become bleed free.

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

Progestogenic side effects may be reduced by using micronised progesterone in the form of oral capsules, transvaginal pessaries or gels. In addition, data from large observational studies have suggested that the risk of VTE and breast cancer with micronised progesterone may be lower compared to that with synthetic progestogens.

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.

If bleeding is heavy or erratic on a sequential regimen, the dose of progestogen can be doubled or duration increased to 21 days.

Persistent bleeding problems beyond six months warrant investigation with ultrasound scan and endometrial biopsy if clinically indicated.

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.

One of the main factors 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.

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

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

Mood swings and PMS-like side effects result from adverse stimulation of the central nervous system progesterone receptors.

The dose can be halved and the 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.

Progesterone is available in an oral micronised form, vaginal pessaries and gel. 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.

The levonorgestrel intrauterine system has a four-year license in the UK for progestogenic opposition of estrogen hormone replacement therapy (five years in other countries). It minimises systemic progestogenic side effects by direct release of progestogen into the endometrial cavity. It is now accepted even in the UK that it can be used for five years for endometrial protection.

Drospirenone, a spironolactone analogue, has anti-androgenic and anti-mineralocorticoid properties. It has been incorporated with low-dose estrogen in a continuous combined formulation.

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 estrogen with or without progesterone has not been effective.

Assessment of serum androgen levels is unlikely to be beneficial as there is poor correlation between circulating androgen levels and clinical symptoms.

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

Testosterone implants and patches have been 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.

Testosterone gels licensed for male use are available in 50 mg, 5 mL sachets or tubes. Unlicensed prescribing by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 to 1.0 mL/day or ¼ sachet/tube on alternate days.

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 DHEA require further research to confirm their efficacy and safety.

Lifestyle/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.

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 (SSRIs) such as paroxetine and fluoxetine and the serotonin and norepinephrine reuptake inhibitors (SNRI) such as venlafaxine in treating vasomotor symptoms. The most common side effect associated with their use is nausea. Fluoxetine and paroxetine should be avoided in tamoxifen users as they interfere with its metabolism and reduce its efficacy.

Handley and Williams 2014 reported a systematic review that included 18 trials assessing the use of antidepressants for vasomotor symptom control. The review concluded that paroxetine, venlafaxine, and desvenlafaxine appeared to be the most effective, with reductions in vasomotor symptoms of over 60% in some trials. Of the latter, paroxetine was noted to have the fewest side effects.

Wei et al. (2016) reported a systematic review and meta-analysis on the effect and safety of paroxetine for vasomotor symptom control. The review included six RCTs with 1571 participants. Paroxetine significantly reduced the frequency of hot flushes by 8.86 per week (95% CI: 5.69–12.04, $p < 0.001$) at 4 weeks and 7.36 per week (95% CI: 4.25–10.46, $p < 0.001$) at 12 weeks. Nausea and dizziness were more common in women taking paroxetine than in those receiving placebo. The review concluded that paroxetine may be appropriate for managing vasomotor symptoms, but there is a need for further research to confirm the most effective and safest dose of paroxetine in this context.

Small studies with the anti-epileptic drug Gabapentin has shown efficacy for hot flush reduction compared to placebo. 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.

Johns et al. (2016) reported a systematic review of randomised trials that assessed non-hormonal interventions for the management of vasomotor symptoms in breast cancer survivors and included 13 trials in the review. Venlafaxine, 75 mg daily, improved hot flushes without additional side effects with higher doses. Gabapentin, 900 mg daily, improved hot flushes more than 300 mg, while Paroxetine 10 mg a day was associated with fewer side effects compared with 20 mg. Venlafaxine was noted to improve hot flush symptoms faster than clonidine. In addition, patient satisfaction with venlafaxine was better than that with gabapentin.

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

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 contraindication to receiving HRT.

Phytoestrogens

Data from some of the better researched phytoestrogen-containing preparations appear to demonstrate some benefits for symptom relief. However, efficacy for vasomotor symptom control is lower than with traditional HRT (approximately 60% symptom reduction compared to 90–100% with traditional HRT).

In addition, there are as yet no hard data on major outcome measures such as coronary heart disease and fractures or long-term endometrial safety with their use beyond two years.

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 use HRT should be made by each woman having been given sufficient information by her health professional to make a fully informed choice.
- 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 particularly in women with risk factors.
- Evidence from observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone may be associated with a lower risk of breast cancer and a lower risk of venous thrombosis compared to that noted with other progestogens.
- 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 estradiol preparation. Evidence from 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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Further reading

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- Climacteric – The Journal of the International Menopause Society, Nick Panay (ed.), Informa Press.
- Maturitas – The Journal of the European Menopause Society, Margaret Rees (ed.), Elsevier Press.
- Management of the Menopause: The Handbook, 5th ed. Rees M et al. (eds), 2009, RSM Press, London.
- Premature Menopause: A Multidisciplinary Approach Eds Singer D Hunter M WileyBlackwell London.

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.pcwfh.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.

Information/support for women

- www.womens-health-concern.org (Women's Health Group – including 'ask the experts').
- www.menopausematters.co.uk (Information on menopause website).
- www.managemymenopause.co.uk (personalised menopausal advice provided by experts).
- www.pms.org.uk (Premenstrual Syndrome website).
- www.nos.org.uk (National Osteoporosis Society – for both professionals and patients).
- www.daisynetwork.org.uk (Premature Menopause Society website).
- www.womens-health-alliance.org.uk (Group of Women's Health Charities).