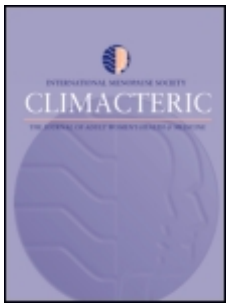

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

R. J. Baber, N. Panay & A. Fenton the IMS Writing Group

To cite this article: R. J. Baber, N. Panay & A. Fenton the IMS Writing Group (2016) 2016 IMS Recommendations on women's midlife health and menopause hormone therapy, Climacteric, 19:2, 109-150, DOI: 10.3109/13697137.2015.1129166

To link to this article: http://dx.doi.org/10.3109/13697137.2015.1129166

CLIMACTERIC, 2016
VOL. 19, NO. 2, 109–150
http://dx.doi.org/10.3109/13697137.2015.1129166

Taylor & Francis
Taylor & Francis Group

RECOMMENDATIONS

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

R. J. Baber, N. Panay, A. Fenton and the IMS Writing Group

ABSTRACT

The International Menopause Society (IMS) has produced these new 2016 recommendations on women's midlife health and menopause hormone therapy (MHT) to help guide health-care professionals in optimizing their management of women in the menopause transition and beyond. The term MHT has been used to cover therapies including estrogens, progestogens and combined regimens. For the first time, the 2016 IMS recommendations now include grades of recommendations, levels of evidence and 'good practice points', in addition to section-specific references. Where possible, the recommendations are based on and linked to the evidence that supports them, unless good-quality evidence is absent. Particular attention has been paid to published evidence from 2013 onwards, the last time the IMS recommendations were updated. Databases have been extensively searched for relevant publications using key terms specific to each specialist area within menopause physiology and medicine. Information has also been drawn from international consensus statements published by bodies such as the IMS, the European Menopause and Andropause Society and the North American Menopause Society. The recommendations have been produced by experts derived mainly from the IMS, with the assistance of key collaborators where deemed advantageous. In preparing these international recommendations, experts have taken into account geographical variations in medical care, prevalence of diseases, and country-specific attitudes of the public, medical community and health authorities towards menopause management. The variation in availability and licensing of MHT and other products has also been considered.

KEYWORDS

Menopause hormone therapy; midlife health; IMS; hormone replacement therapy; HRT; Recommendations

Introduction

The International Menopause Society (IMS) is pleased to provide these new evidence-based recommendations on the use of menopausal hormone therapy (MHT). In the 3 years that have passed since publication of our 2013 Recommendations, new research into the health of midlife women and re-evaluation of existing data have allowed clinicians world-wide to gain more clarity into the role of MHT, not only in the alleviation of troublesome menopausal symptoms, but also in the prevention of diseases of aging. A key turning point in this process was the IMS-sponsored Global Consensus Meeting held in Paris in November 2012 and the subsequent publication of a concise Global Consensus Statement supported by major societies interested in the health and well-being of midlife women.

It is timely that these new, detailed 2016 IMS Recommendations have been published. The format of these Recommendations has changed since the 2013 publication. Each section now contains a brief summary of the key points of the topic and a summary of the way in which evidence used was identified and assessed. Importantly, these Recommendations now include grades of recommendations, levels of evidence and some practical 'Good practice points'. It is important to note that the evidence supporting these recommendations is derived from research largely performed on women living in Western countries. This may not necessarily be directly applicable to other women. Of course, references are included.

Throughout the Recommendations, the term MHT has been used to cover therapies including estrogens, progestogens and combined therapies. The IMS is aware of the geographical variations related to different priorities of medical care, different prevalence of diseases, and country-specific attitudes of the public, the medical community and health authorities toward menopause management, different availability and licensing of products, all of which may impact on MHT. These Recommendations and the subsequent key messages therefore give a simple overview that serves as a common platform on issues related to the various aspects of hormone therapy, which

CONTACT Professor R. J. Baber rod@rodbaber.com.au Obstetrics and Gynaecology, Sydney Medical School North, The University of Sydney, Sydney, Australia

could be easily adapted and modified according to local needs.

Methodology

This guideline was produced by a body of experts derived primarily but not exclusively from the IMS. Medline, PubMed, the Cochrane register of controlled trials and other databases were extensively searched for relevant publications using key terms specific to each specialist area within menopause physiology and medicine. Information was also drawn from international consensus statements published by bodies such as the IMS, the European Menopause and Andropause Society (EMAS) and the North American Menopause Society (NAMS). Particular attention was paid by the authors to the new publications from 2013 onwards which was the last time the IMS Recommendations were updated.

The definitions of types of evidence used in this guideline are detailed in the Governance advice No. 1 of the Royal College of Obstetricians and Gynaecologists[1]. Table 1 shows the definitions for levels of evidence (<1++> to <4>) and grades of recommendations ([A], [B], [C] or [D]) used when assessing the value of data and strength of recommendations in each section. Where possible, recommendations are based on and linked to the evidence that supports them unless good-quality evidence is absent. Areas where advice has been issued in the absence of good evidence, but based on extensive experience, are annotated as good practice points, indicated by ☑.

The authors have strived for a consistent style of assessment and reporting through the issuing of explicit guidelines to the section authors at the start of the guideline process. Nonetheless, given the multi-author nature of this document, there will inevitably be some variation in the consistency with which the data have been reported and interpreted.

IMS governing principles on MHT

- MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy.
- Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction (including reduced libido) may improve during MHT.
- Quality of life and sexual function may also improve.
- The administration of individualized MHT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life.
- Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women.
- MHT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations.
- The risks and benefits of MHT differ for women during the menopause transition compared to those for older women.

Table 1. Levels of evidence and Grades of recommendations (taken from the Royal College of Obstetricians and Gynaecologists UK Green Top Guidelines).

Classification of evidence levels		*Grades of recommendations*	
<1++>	High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias	[A]	At least one meta-analysis, systematic review or randomized controlled trial rated as 1++, and directly applicable to the target population; *or* a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
<1+>	Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a low risk of bias	[B]	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or* extrapolated evidence from studies rated as 1++ or 1+
<1−>	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias	[C]	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or* extrapolated evidence from studies rated as 2++
<2++>	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	[D]	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
<2+>	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal		
<2−>	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal		
<3>	Non-analytical studies, e.g. case reports, case series		
<4>	Expert opinion		
☑	**Good practice point**: Recommended best practice based on the clinical experience of the guideline development group		

- MHT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Thus, the term 'class effect' is confusing and inappropriate. However, evidence regarding differences in risks and benefits between different products is limited.
- Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. MHT may reduce symptoms and preserve bone density and is advised at least until the average age of menopause.
- Counselling should convey the benefits and risks of MHT in clear and comprehensible terms, e.g. as absolute numbers rather than, or in addition to, percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about MHT. Written information about risks and benefits as well as decision aids may be useful.
- MHT should not be recommended without a clear indication for its use, i.e. significant symptoms or physical effects of estrogen deficiency.
- Women taking MHT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening.
- There are no reasons to place mandatory limitations on the duration of MHT. Data from the WHI trial and other studies support safe use for at least 5 years in healthy women initiating treatment before age 60.
- Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks.
- The dosage should be titrated to the lowest effective dose.
- Lower doses of MHT than previously used may reduce symptoms sufficiently and maintain quality of life for many women. However, long-term data on lower doses regarding fracture or cancer risks and cardiovascular implications are still lacking.

Midlife body changes

Weight gain at midlife is often attributed to hormonal changes at menopause. However, both cross-sectional and longitudinal studies have consistently shown this not to be the case[1–3]. The steady weight gain, of about 0.5 kg per year, seen in women at midlife is associated with age and environmental factors, not menopause. <2++> Variables associated with a greater likelihood of obesity in women at midlife include urbanization, lower level of education, inactivity, higher parity, family history of obesity and marriage at earlier age[4,5]. Disruption of the circadian rhythm by shift work and sleep deprivation also contributes to weight gain[6]. The relationship between depression and midlife weight gain is bidirectional[7]. <2+>

The change in the hormonal milieu at menopause is associated with significant increases in waist circumference[8] and central abdominal fat[9,10]. Increased waist circumference occurs in relation to final menstrual period[8] and significant increases in central abdominal fat have been seen in longitudinal studies of Caucasian and Asian women[9,10]. Total mass, percentage fat mass, truncal fat mass and visceral fat also increase in non-obese women across the menopausal transition[10]. The redistribution of fat to the abdomen results in a transition from a gynoid to an android pattern of fat distribution[11]. Studies using a range of radiological modalities have shown that postmenopausal women have greater amounts of intra-abdominal fat compared to premenopausal women[12,13]. Waist circumference represents both subcutaneous and visceral adipose tissue depot size and correlates closely with cardiovascular disease risk. In women, it is also closely associated with dyslipidemia[14]. Animal models show that estrogen depletion favors central abdominal fat accumulation and that this is ameliorated by estrogen therapy[15,16]. <2++>

Governing principles for managing midlife body changes

The primary approach to minimize weight gain at midlife is caloric restriction and maintenance of physical activity[17].

Management of factors associated with weight gain, such as depression, is important. If depression requires pharmacotherapy, medications associated with weight gain commonly used such as clozapine, imipramine, and amitriptyline should be avoided if possible[18].

Most randomized, controlled trials (RCTs) show a reduction in central adiposity with estrogen therapy[19–22]. <1++> In a subsample of participants in the Women's Health Initiative (WHI) estrogen plus progestin

therapy (E + P) study, the E + P intervention at 3 years significantly helped to maintain lean body mass and prevented a shift toward android fat distribution[21]. The effects of exogenous estrogen are generally favorable in terms of body composition; however, the route of estrogen delivery may have subtle, but differing effects[23,24]. Oral estrogen has been associated with a small but significant increase in fat mass and a decrease in lean mass, whereas lean body mass and fat mass are unaffected by transdermal estradiol[23,24]. Neither route appears to alter visceral fat mass[24]. The different effects of oral versus transdermal estrogen may relate to the effects of route of administration on growth factors and substrate oxidation[17].

Summary

Weight management and prevention of weight gain are essential components in the care of postmenopausal women. Optimizing body weight should be considered early in the perimenopause to safeguard the quality of life of women. The primary approach to weight management should be encouragement of a healthy diet and physical activity. Contrary to widespread belief, menopausal hormone therapy is not associated with weight gain and may ameliorate perimenopausal accumulation of abdominal fat.

Key messages

- An absolute increase in weight at midlife is not attributable to the menopause. [B]
- The hormonal changes that accompany menopause are associated with increases in total body fat and abdominal fat, even in lean women. [B]
- Maintenance of a healthy diet and avoidance of caloric excess combined with physical activity are important components of weight management.
- Menopausal abdominal fat accumulation is ameliorated by estrogen therapy, with a reduction in overall fat mass, improved insulin sensitivity and a lower rate of development of type 2 diabetes. [A]

Diagnosis of menopause

Information is mainly derived from consensus rather than data and therefore statements are mainly supported by Good Practice Points.

Definition

Menopause is defined as the final menstrual period. Menopause is a retrospective clinical diagnosis, as the final menstrual period can only be defined if followed by 12 months of amenorrhea.

Menopause before the age of 40 years is considered to be premature, whether occurring naturally or as a result of surgery or some other intervention (e.g. chemotherapy). The clinical implications of menopause before age 40 are different from menopause after age 40. Treatment of premature menopause is typically considered more critical (see section on Premature ovarian insufficiency).

Menopause is a natural and inevitable event that happens on average at age 51 years in white Caucasians with ethnic and regional variations.

Stages of Reproductive Aging Workshop + 10

Accurate staging of reproductive aging is important from a clinical and research perspective. The gold-standard criteria for staging reproductive aging were defined by the Stages of Reproductive Aging Workshop + 10 (STRAW + 10)[1] (see Figure 1).

Antral follicle count, follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin B are included as supplementary criteria. They are of greater importance to the fertility specialist and are not essential in the diagnosis of menopause. Specific cut-off values for AMH and inhibin B were not proposed given the lack of international standardization for those hormonal assays.

The criteria also identify the stages at which vasomotor symptoms (VMS) and urogenital atrophy are evident, although menopausal symptoms are not used in determining stage.

Standard terminology is used to identify three broad stages of reproductive aging (Reproductive, Menopausal Transition, and Postmenopause), each broken down further into Early, Peak (reproductive stage only) and Late stages. Altogether, there are a total of ten specific stages, labeled from −5 to +2. Stage −1, for example, corresponds to the late stage of the menopausal transition, with the principal criterion of an interval of amenorrhea of > 60 days and other supportive criteria such as FSH > 25 IU/l (see Figure 1).

STRAW + 10 guidelines recommend waiting at least 3 months after surgery to assess supportive endocrine criteria, because evidence suggests that FSH levels rise temporarily following pelvic surgery[2].

Although VMS are the cardinal symptoms of menopause, they should not be used to stage women because VMS are reported in the reproductive stage and may last for many years after the final menstrual period[3,4].

STRAW + 10 was sponsored by the National Institute on Aging, the Office of Research on Women's Health, NAMS, the American Society for Reproductive Medicine

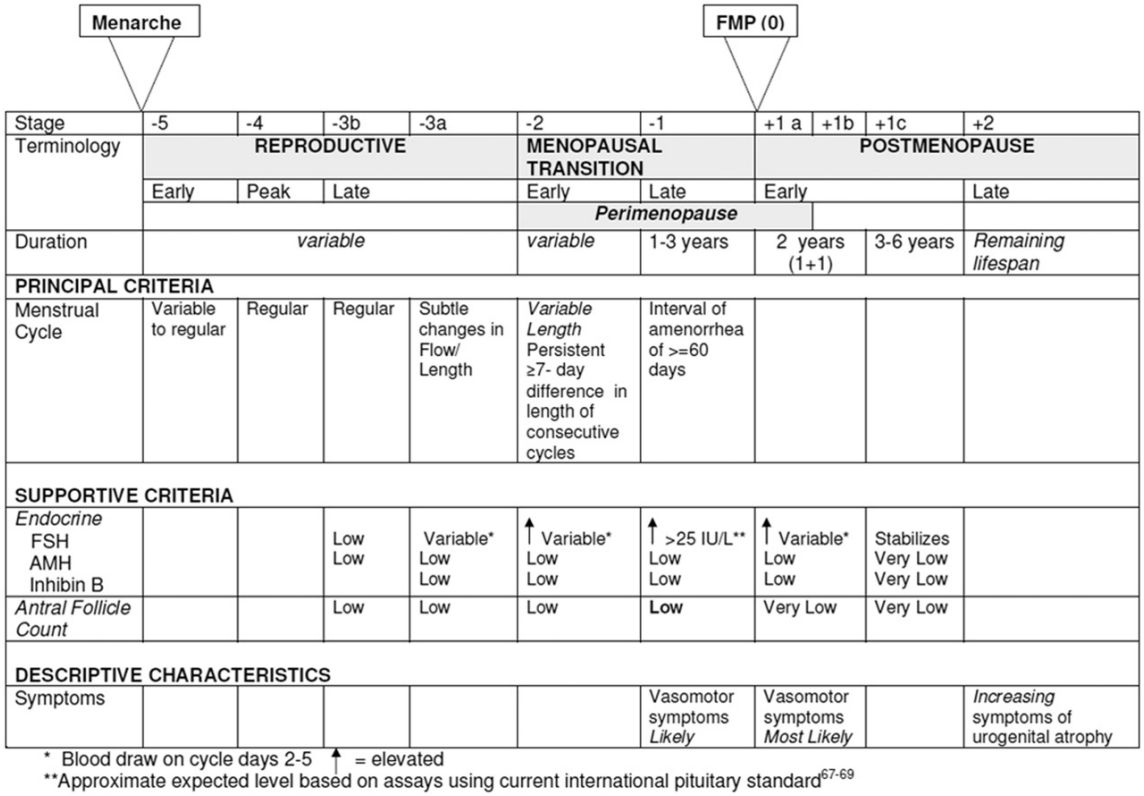

Figure 1. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. FMP, final menstrual period; FSH, follicle stimulating hormone; AMH, anti-Müllerian hormone. Reprinted from Harlow SD, Gass M, Hall JE, *et al*. Executive Summary: Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Climacteric* 2012;15:105–14; *Fertil Steril* 2012;97:843–51; *J Clin Endocrinol Metab* 2012;97:1159–68; *Menopause* 2012;19:387–95.

(ASRM), the IMS, and the Endocrine Society. The criteria for STRAW + 10 were the result of a 2-day in-person meeting of international experts hosted at the 2011 Annual Meeting of NAMS[1]. The criteria built on original menstrual cycle criteria from the 2001 Stages of Reproductive Aging Workshop (STRAW)[5] and the ReSTAGE Collaboration, which validated the criteria based on empirical analyses of four cohort studies[6–9].

Key messages

- Current data indicate that the STRAW + 10 criteria apply to most, but not all women.
- The criteria cannot be used in women with polycystic ovarian syndrome and premature ovarian insufficiency and those who have had endometrial ablation or removal of a single ovary and/or hysterectomy. In such women, the supportive criteria should be used to determine reproductive stage. ☑
- With the availability of new multi-ethnic studies[9–14], STRAW + 10 provided support for the generalizability of RESTAGE to ethnically diverse women, as well as to smokers and obese women. [B]
- STRAW + 10 principally relies on changes in bleeding patterns as staging criteria with the last menstrual period as the pivotal point. ☑

Premature ovarian insufficiency

Background and introduction

Premature ovarian insufficiency (POI) (also known as premature menopause) is defined as primary hypogonadism before the age of 40 years in women with a normal karyotype who previously had normal menstrual cycles. It is characterized by typical menopausal symptoms and signs, oligomenorrhea or amenorrhea and FSH >40 IU/l.

The diagnosis of POI should only be confirmed after a minimum of two elevated FSH test results (>40 IU/l) at least 4–6 weeks apart.

The incidence of spontaneous POI is 1% of women under the age of 40 years and 0.1% of women under the age of 30 years[1]. <2++>

The incidence of iatrogenic POI may be growing due to increasing survival rates following chemo- and radiotherapy.

Women with POI are now recognized to be at increased risk for premature morbidity and mortality. They have impaired endothelial function[2], ischemic heart disease[3], ischemic stroke[4], a higher incidence of osteoporotic fractures[5], impaired cognition[6] and diminished sexual well-being[7]. <2+>

Etiological factors

POI may be either primary or secondary. In the majority of cases of primary POI, the cause is unknown. The causes of POI[8] are shown in Table 2. <1++>

Karyotype methodology has detected monosomy X, mosaicism, X chromosome deletions and rearrangements, X-autosome translocations, and isochromosomes in women with POI[9].

Candidate gene studies have detected a number of single gene perturbations predisposing to POI in at least one population. A meta-analysis of gene variations and POI showed that bone morphogenetic protein 15 538A (BMP 15 538A), Fragile X mental retardation 1 (FMR1) premutation on the X chromosome and inhibin alpha 769 (INHA 769) (in Asians alone) may indicate susceptibility to POI[10]. <1++> Other likely candidate genes include progesterone receptor membrane component 1 (PGRMC1), growth differentiation factor 9 (GDF9) and newborn ovary homeobox gene (NOBOX)[9].

Studies performed in Serbian women showed that estrogen receptor (ER) α gene polymorphism is not associated with POI[11]. Ethnically distinct populations may show differences in gene-regulating pathways and genes causing POI, like in Han Chinese vs. Serbian women for tested loci: 8q22.3, HK3, BRSK1[12]. <2+>

Whole genome approaches, e.g. genome wide association studies (GWAS), are currently being used to reveal loci not predicted by candidate genes.

Polyglandular autoimmune diseases can be found in some women with POI. Autoimmune hypothyroidism, diabetes mellitus, adrenal insufficiency and hypoparathyroidism occur more frequently in women with POI compared to background rates[13]. <2+>

Management

Management should include detailed history taking including family history, vaginal examination, hormone analysis, karyotyping, fragile X, thyroid and adrenal antibody assays and ultrasound scanning (Table 3).

Information on hot flushes, vaginal dryness, lack of libido, arthralgia, loss of concentration, insomnia and fertility issues should be obtained in a sensitive and caring manner.

Table 2. Known causes of premature ovarian insufficiency.

Primary
Genetic
chromosome abnormalities
FMR1 premutations
other gene candidates
Enzyme deficiencies
Autoimmune diseases
Secondary
Chemotherapy and radiotherapy
Bilateral oophorectomy or surgical menopause
Hysterectomy without oophorectomy/uterine artery embolization
Infections

Table 3. Investigations of premature ovarian insufficiency.

- Hormone analysis: FSH, LH, estradiol, AMH, inhibin B, prolactin, testosterone, free thyroxine, TSH, cortisol, ACTH, DHEAS
- Autoimmune screen for polyendocrinopathies
- Chromosome analysis for women younger than 30 years
- Pelvic and breast ultrasound
- Dual X-ray absorptiometry (optional)

FSH, follicle stimulating hormone; LH, luteinizing hormone; AMH, anti-Müllerian hormone; TSH, thyroid stimulating hormone; ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate

The diagnostic usefulness of ovarian biopsy outside the context of a research setting is unproven.

Therapeutic options

Women with POI should receive hormonal treatment after exclusion of contraindications; they usually need higher doses of estrogens compared to women over 40 years old. The recommended estrogen doses are: 17β-estradiol 2 mg/day or 1.25 mg conjugated equine estrogen (CEE) or transdermal estradiol 75–100 μg/day or 10 μg ethinylestradiol[14]. The aim is to achieve the typical mean serum estradiol levels of approximately 100 pg/ml (400 pmol/l) in regularly menstruating women[15]. Micronized progesterone can be administered as a cyclic regimen (200 mg for 12 days each month) or as a continuous regimen of 100 mg per day, typically > 2 years post final menstrual period.

Combined estrogen/progestogen contraceptive pills (COCs) may be used continuously until the expected time of the menopause but data are lacking regarding impact on bone and cardiovascular disease. Data from small randomized trials of surrogate markers suggest that bone mineralization and metabolic effects are more favorable with MHT compared to COCs. <1−>

Hormone therapy is not contraceptive unless estrogen is combined with a levonorgestrel intrauterine system; it may therefore be more practical for the COC to be used for the first few years following diagnosis of POI in those wishing to avoid pregnancy.

In women with low libido, especially in oophorectomized women, testosterone gels or patches could be prescribed <2++>; however, due to the lack of licensed female options, down titration of male products may be necessary (see section on Androgens).

Women with POI have a 5–15% chance of spontaneous conception after confirmation of diagnosis. Inappropriate follicular luteinization is the most common pathophysiological mechanism that prevents ovulation and pregnancy[16].

Exogenous estrogens have beneficial effects on ovulation and fertility. However, ovulation only seems to occur in women whose serum FSH concentrations are suppressed to below 15 IU/l[17]. Gonadotropin therapy is ineffective in achieving ovulation and gonadotropin releasing hormone agonists do not improve ovulatory rates. <2+>

Donor oocyte *in vitro* fertilization is a successful treatment choice for women with POI. <1+>

In women undergoing chemotherapy or radiotherapy, *in vitro* fertilization (IVF) with embryo freezing prior to treatment offers the highest likelihood of a future pregnancy[18].

Freezing of mature eggs is less successful than embryo freezing. <3>

Cryopreservation and transplantation of fresh ovarian tissue are leading to an increasing number of successful pregnancies. <3>

A meta-analysis (24 articles from 1980 to 2013) of ovarian transposition in women with cancers has shown that ovarian transposition is associated with significant preservation of ovarian function[19]. <1+>

Key messages

- POI is defined as primary hypogonadism in women younger than 40 years who previously had menstrual cycles.
- The diagnosis of POI is confirmed by the finding of FSH levels >40 IU/l on two occasions 4–6 weeks apart.
- POI should be effectively treated to prevent an increase in the risk of cardiovascular disease, osteoporosis, cognitive decline, dementia and Parkinsonism. [B]
- Investigation of POI should include hormone analysis, screening for autoimmune causes, karyotyping, fragile X premutation testing and pelvic ultrasound. ☑
- It is important to inform the woman of the diagnosis with empathy in a sensitive and caring manner. Women must be provided with adequate information and counseling. ☑
- The mainstay of treatment is hormone replacement with estrogen, progesterone and possibly testosterone which needs to be continued at least until the average age of the natural menopause. [B]
- Hormone treatment with COC or MHT can induce ovulation in POI patients if FSH levels are suppressed. [C]
- MHT should not be regarded as being contraceptive. ☑
- Ovarian stimulation with drugs such as clomiphene citrate and gonadotropin therapy should not be routinely used as they have no proven benefit. [B]
- IVF with donor oocytes/embryos has a high success rate [A] but is not acceptable to all women with POI. ☑

Lifestyle, diet and exercise

The public health approach to lifestyle promotion requires a multidisciplinary approach, starting from schools through to work places, involving the food and advertising industry, as well as medical insurers and health authorities. A new paradigm in doctor–patient relations is required, where the doctor becomes more of an advisor and the patient takes responsibility for his/her own health.

Improved metabolic profile, balance, muscle strength, cognition and quality of life are observed in physically active women. <2+> Heart events, stroke, fractures and breast and colon cancers are significantly less frequent. <2+> The benefits of exercise far overweigh possible adverse consequences: the more, the better, but too much may cause harm[1]. <1+>

Obesity (body mass index >30 kg/m^2) affects over 20% of the population in many parts of the world and is becoming an increasing problem in the lower socioeconomic sectors and also among children. It can be associated with insulin resistance and thus increases not only a woman's risk of cardiovascular disease and diabetes, but also increases the risk for breast, colon and endometrial cancers[2]. <2++>

Key messages

- Regular exercise is advised to reduce cardiovascular and total mortality. [B]
- Optimal exercise prescription is at least 150 minutes of moderate-intensity exercise per week. Two additional weekly sessions of resistance exercise may provide further benefit. [B]

- The recommended intensity of aerobic activity should take into account the older adult's aerobic fitness. ☑
- Weight loss of only 5–10% is sufficient to improve many of the abnormalities associated with the insulin resistance syndrome. [B]
- The basic components of a healthy diet are: several servings/day of fruits and vegetables, whole grain fibers, fish twice per week, and low total fat (but the use of olive oil is recommended). Consumption of salt should be limited and the daily amount of alcohol should not exceed 30 g for men and 20 g for women. ☑
- Smoking should be avoided. [A]
- Lifestyle modifications include socializing and being physically/mentally active. ☑

Urogynecology

The female genital and lower urinary tracts share a common embryological origin, arising from the urogenital sinus and both are sensitive to the effects of female sex steroid hormones throughout life[1]. Estrogen is known to have an important role in the function of the lower urinary tract and estrogen and progesterone receptors have been demonstrated in the vagina, urethra, bladder and pelvic floor musculature. Consequently, exogenous estrogen therapy may be useful in the management of pelvic floor dysfunction. <2>

Urinary incontinence

The role of systemic estrogens in the management of postmenopausal women with lower urinary tract symptoms has been investigated in three large epidemiological studies examining the use of combined estrogen/progestogen and estrogen-only systemic hormone replacement therapy[2–4]. In all of these trials, systemic estrogen replacement therapy was found to increase the risk of developing both stress and urgency urinary incontinence, and, in those women who complained of urinary incontinence at baseline, the symptoms were found to deteriorate. This was also reflected in deterioration in quality of life.

The most recent meta-analysis of the effect of estrogen therapy on the lower urinary tract has been performed by the Cochrane group[5] and identified 33 trials, including 19 313 incontinent women (1262 involved in trials of local administration) of whom 9417 received estrogen therapy. Systemic administration (of unopposed oral estrogens – synthetic and CEE) resulted in worse incontinence than placebo (relative risk (RR) 1.32; 95% confidence interval (CI) 1.17–1.48), although this is heavily influenced by the size of the WHI study[6]. When considering combination therapy, there was a similar worsening effect on incontinence when compared to placebo (RR 1.11; 95% CI 1.04–1.18). There was some evidence suggesting that the use of local estrogen therapy may improve incontinence (RR 0.74; 95% CI 0.64–0.86) and overall there were one to two fewer voids in 24 h and less frequency and urgency. <1+>

Overactive bladder

Lifestyle changes and bladder retraining have been shown to be effective for overactive bladder symptoms[6]. <1+> In a review of ten randomized, placebo-controlled trials, systemic estrogen was not found to be superior to placebo when considering symptoms of urgency, frequency and nocturia, although vaginal estrogen administration was found to be superior to placebo for the symptom of urgency[7]. There is also evidence to suggest that combination therapy with an antimuscarinic drug may be beneficial[8] and the current guidelines from the International Consultation on Incontinence (ICI) also suggest that local estrogen therapy may have a role[9]. <2+>

Stress urinary incontinence

Data show that all women complaining of stress urinary incontinence will benefit from pelvic floor muscle training in the first instance[6]. <1+> Duloxetine may work synergistically with conservative therapy[8] <2+>, although some women will ultimately require surgery, and retropubic and trans-obturator tapes are currently the most popular procedures[10]. <1+>

A review of eight controlled and 14 uncontrolled prospective trials concluded that estrogen therapy was not an efficacious treatment for stress incontinence but may be useful for symptoms of urgency and frequency[11]. This is supported by the findings of the ICI[9]. <2+>

Estrogens in the management of recurrent urinary tract infection

Estrogen therapy has been shown to decrease vaginal pH and reverse the microbiological changes that occur in the vagina following the menopause[12] and has been shown to be useful in the prevention of recurrent urinary tract infections[13,14]. A Cochrane review has investigated the role of estrogens in the management of recurrent lower urinary tract infections in nine studies including 3345 women. Oral estrogens were found to be ineffective (RR 1.08; 95% CI 0.88–1.33). Two

small studies found that vaginal estrogens reduced the number of infections when compared to placebo (RR 0.25; 95% CI 0.13–0.50; and RR 0.64; 95% CI 0.47–0.86, respectively)[15]. <1+>

Urogenital atrophy

Whilst the evidence supporting the use of estrogens in lower urinary tract dysfunction remains controversial, there are considerable data to support their use in urogenital atrophy[16] and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritis and dyspareunia, and greater improvement in cytological findings[17]. The most recent meta-analysis of intravaginal estrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2003[18]. Sixteen trials with 2129 women were included and intravaginal estrogen was found to be superior to placebo in terms of efficacy, although there were no differences between types of formulation. Fourteen trials compared safety between the different vaginal preparations and found a higher risk of endometrial stimulation with conjugated equine estrogens as compared to estradiol. <1+>

Key messages

- Symptoms such as vaginal dryness, soreness, dyspareunia, urinary frequency, nocturia and urgency are extremely common in postmenopausal women.
- Incontinence in women increases in prevalence with age.
- There is a wide variation in symptoms and signs of urogenital aging.
- The loss of lubrication and hormonal changes may lead to sexual dysfunction. Treatment of this condition improves quality of life, not only for the woman but also for her partner.
- Urogenital symptoms respond well to estrogens. [A]
- Long-term treatment is often required as symptoms can recur on cessation of therapy. Systemic risks have not been identified with local low-potency/low-dose estrogens. [B]
- Use of systemic MHT does not seem to prevent urinary incontinence and is not preferable to low-dose local estrogens in the management of urogenital atrophy or recurrent lower urinary tract infections. [B]
- Lifestyle changes and bladder retraining are recommended as first-line therapy for overactive bladder symptoms. ☑
- Antimuscarinic drugs, combined with local estrogens, constitute first-line medical treatment in postmenopausal women with symptoms suggestive of an overactive bladder. [A]
- All women complaining of stress urinary incontinence will benefit from pelvic floor muscle training in the first instance. ☑
- Duloxetine may work synergistically with conservative therapy. However, some women will ultimately undergo surgery, and retropubic and transobturator tapes are currently the most popular procedures.
- There is currently no role for systemic estrogen therapy in women with pure stress urinary incontinence. [A]

Postmenopausal osteoporosis

Osteoporosis is a systemic skeletal disease characterized by diminished bone strength with the risk of sustaining a fracture when falling from own body height (fragility fracture). Bone strength is determined by a combination of bone density and microarchitectural integrity. Postmenopausal osteoporosis results from a failure to attain peak bone density, accelerated bone loss after menopause, age-related bone loss or a combination of factors. Accelerated postmenopausal bone loss is induced by estrogen deprivation.

Although skeletal health is a function of genetic predisposition, it can be modified by lifestyle factors such as diet, weight-bearing exercise and the avoidance of bone-toxic substances[1]. <1+>

Hip fracture is responsible for the largest proportion of the financial burden of osteoporosis to health-care systems but other osteoporosis-related fractures, particularly vertebral fractures, cause considerable morbidity[2]. <1+>

Diagnosis and assessment

The diagnosis of osteoporosis is based on assessment of bone mineral density (BMD) by dual X-ray absorptiometry (DXA). The value obtained is compared to peak bone density and expressed as the *T*-score. Osteoporosis is defined as a *T*-score ≤ -2.5 or the presence of a fragility fracture. Assessment of BMD is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors such as a personal or family history of fractures, history of amenorrhea, primary ovarian insufficiency, low body mass, diet, smoking, alcohol abuse, the use of bone toxic medication and rheumatoid arthritis[3]. <1+> The 10-year probability of fracture in an individual can be estimated

using a model that integrates various risk factors for fracture, such as the FRAX® model developed by the World Health Organization, which is available online at www.sheffield.ac.uk/FRAX/. <1+> It should be noted that the sensitivity of the FRAX model in early menopause has been questioned as being lower compared to sensitivity in older women[4]. An appropriate assessment of prevalent fractures and secondary causes of osteoporosis should precede any therapeutic decisions.

Treatment

The goal of osteoporosis treatment is the prevention of fracture. Choice of therapy should be based on a balance of effectiveness, risk and cost. Intervention thresholds for therapy can be based on 10-year fracture probability but will be country-specific. Alternatively, treatment can be given to all patients with a fragility fracture or a *T*-score of ≤ -2.5 (osteoporosis), or a *T*-score of $< -1.0 > -2.5$ (osteopenia) with additional risk factors. Monitoring of therapy by serial DXA should be interpreted with caution and take into account the site monitored, time interval, drug-specific expectations and the value of least significant change as calculated for the specific device and operator.

Therapeutic options

Menopausal hormone therapy

MHT decreases the incidence of all fractures, including vertebral and hip fractures, even in women not at high risk of fracture[5]. <1++> MHT is the only therapy available with proven efficacy of fracture reduction in patients with osteopenia.

Although MHT prevents fractures at any age after the menopause, age at the initiation of MHT is important[6]. In the age group 50–60 years or within 10 years after menopause, the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy[7]. <1+> Initiation of MHT in the age group 60–70 years requires individually calculated benefit/risk, consideration of other available drugs and the lowest effective dose[8]. <1+> MHT should not be initiated after age 70 years. There is no mandatory time limit for duration of MHT provided that it is consistent with treatment goals. <4> This is important as the protective effect of MHT on BMD declines after cessation of therapy at an unpredictable rate, although some degree of fracture protection may remain after cessation of MHT[9]. <1+> Therefore, the continuation of MHT for the sole purpose of the prevention of fractures should take into account the risk of fracture as well as other possible long-term benefits and risks. Evidence for the fracture-protective effect of MHT is limited to standard dosages of CEE and medroxyprogesterone acetate (MPA), given by the oral route. Evidence for protection against loss of BMD is available for lower than standard doses in oral (CEE and 17β-estradiol) and transdermal (17β-estradiol) administration[10]. <1+>

Tibolone, a synthetic preparation metabolized to molecules that have affinity for the estrogen, progesterone and androgen receptors prevented vertebral and non-vertebral fractures in a RCT[11]. <1+>

In women with a uterus, the stimulatory effects of CEE on the endometrium can be opposed by the selective estrogen receptor modulator (SERM) bazedoxifene. This combination, also known as tissue selective estrogen complex, has been shown to prevent the bone loss associated with menopause but the effect on fracture reduction has not been explored[12]. <1+>

Calcium and vitamin D

Postmenopausal women need a dietary reference intake (DRI) of 1000–1500 mg of elemental calcium. Calcium supplementation should be restricted to bridge the shortfall between dietary intake and the DRI and to patients being treated for high fracture risk[13]. <4> Routine dietary calcium supplementation cannot be justified in terms of efficacy, safety and health economics. Excessive calcium supplementation may be associated with increased cardiovascular risk, renal calculi and constipation[14]. <2−>

The DRI for vitamin D is 800–1000 IU in the postmenopausal period. As the major source of vitamin D is dependent on sunlight exposure, the need for supplementation will vary. Measuring the blood 25-hydroxyvitamin D level may be helpful in selected individuals[15]. <4> Vitamin D supplementation has been shown independently to lower the risk of fracture and of falling in elderly patients[16]. <2−>

Bisphosphonates

The bisphosphonates are potent inhibitors of bone resorption with proven efficacy in the prevention of vertebral and hip fractures[17,18]. <1++> Some safety issues are relevant. An association has been suggested between atypical femur shaft fractures and over-suppression of bone turnover in patients exposed to bisphosphonates for longer than 3–5 years. A drug-free period may be considered after 3 years of intravenous zoledronic acid or 5 years of oral alendronate therapy, provided that BMD increases to a DXA-derived *T*-score of > -2.5 and in the

absence of any fracture[19]. <4> Bisphosphonate-related osteonecrosis of the jaw is a rare complication and generally is only a risk when dosages greater than that recommended for fracture prevention are used[20]. <4> There is no evidence that bisphosphonates prevent fractures in osteopenic patients.

Selective estrogen receptor modulators

The SERMs, raloxifene and bazedoxifene, reduce vertebral fractures in postmenopausal women with or without prevalent vertebral fractures[21]. <1+> Bazedoxifene prevents hip fracture in a select group of women at high risk of hip fracture[22]. <1−> Raloxifene prevents ER-positive breast cancer in osteoporotic women. The SERMs do not alleviate vasomotor symptoms associated with menopause.

Parathyroid hormone

Parathyroid hormone (PTH) is an anabolic agent that significantly reduces risk of vertebral fractures by stimulation of bone formation[23]. <1+> PTH is indicated for severe cases of osteoporosis or in patients who fracture while on other forms of therapy. PTH is given as a daily subcutaneous injection for a maximum of 18 months. After this period, the use of an antiresorptive agent must be considered. Use of PTH is limited by the cost being much higher than that of other available agents. Prior treatment with a bisphosphonate blunts the effect of subsequent PTH.

Strontium ranelate

Treatment with strontium ranelate significantly reduces the risk of vertebral and non-vertebral fractures in osteoporotic patients, irrespective of the presence of a fracture or age[24]. <1+> Recent concerns about cardiovascular safety have limited the use of strontium ranelate to cases of severe osteoporosis in patients at low risk of cardiovascular disease[25]. <2−>

Denosumab

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANKL). At a dose of 60 mg subcutaneously 6-monthly, denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures[26]. <1++> Denosumab is generally safe and well tolerated.

Key messages

- Osteoporosis is a systemic skeletal disease characterized by diminished bone strength with the risk of sustaining a fracture when falling from own body height.
- Osteoporosis is defined as a DXA-derived *T*-score ≤ -2.5 or the presence of a fragility fracture.
- The 10-year probability of fracture in an individual can be estimated using a model that integrates various risk factors for fracture, such as the FRAX® model. [A]
- Intervention thresholds for therapy can be based on 10-year fracture probability but will be country-specific.
- Alternatively, treatment can be given to all patients with a fragility fracture or a *T*-score of ≤ -2.5 (osteoporosis), or a *T*-score of $< -1.0 > -2.5$ (osteopenia) with additional risk factors. [A]
- An appropriate assessment of prevalent fractures and secondary causes of osteoporosis should precede any therapeutic decisions.
- Lifestyle changes should be part of treatment strategy. [A]
- Choice of pharmacological therapy should be based on a balance of effectiveness, risk and cost.
- MHT is the most appropriate therapy for fracture prevention in the early menopause. [A]

Skin, cartilage, connective tissues

The effects of estrogen in bone are well characterized but data on the impact of estrogen on cartilage, skin and connective tissues have been slower to emerge.

Cartilage

Although no clear association has been found between lifetime estrogen exposure and the risk of osteoarthritis <2+>, generalized muscle and joint aches are among the commonest symptoms experienced by women at menopause[1]. <1+> Intervertebral discs are thinner after menopause and women show greater increases in the prevalence and incidence of osteoarthritis when compared to men. Furthermore, arthritis in women is more likely to be progressive and symptomatic. <2+>

Estrogen receptors ERα and ERβ have both been identified in chondrocytes and recent studies have also demonstrated estrogen receptors in synoviocytes. Several animal and pre-clinical studies have demonstrated protective effects on the cartilage from the use of estrogen[2]. Cartilage degradation has been shown to be less in women taking the SERM levormeloxifene or MHT[3]. The WHI has also demonstrated a 45% reduction in total joint surgery among women taking MHT compared to placebo[4]. <1+>

Skin

Estrogen receptors have been detected in many skin elements including keratinocytes, melanocytes, fibroblasts, hair follicles and sebaceous glands so it is likely that the withdrawal of estrogen at menopause will have measurable effects on skin health. Studies have shown that after menopause skin thins and there is a loss of viscoelasticity. Skin surface texture, water-holding capacity, collagen content of the dermis and viscoelasticity have shown improvement with the use of estrogen[5,6]. <1+>

Ligaments and tendons

The effect of estrogen on the function and health of ligaments and tendons is not fully elucidated. Lower tendon stiffness, trends towards higher fibril density and higher collagen turnover have been described in women on MHT[7]. <1+>

Key messages

- Estrogen has an effect on connective tissue throughout the whole body. [A]
- The marked predominance of polyarticular osteoarthritis in women and, in particular, the marked increase of osteoarthritis in women after the menopause suggests that female sex steroids are important for cartilage homeostasis. [B]
- Cartilage degradation and the need for joint replacement surgery are reduced among users of MHT. [A]
- Menopause is associated with a number of changes in skin health that may be reduced with the use of MHT or topical estrogen therapy. [A]

Cardiovascular disease

Cardiovascular disease is the principal cause of morbidity and mortality in postmenopausal women. Major primary prevention measures are smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise and diabetes and lipid control[1]. <1−> Primary prevention strategies which are effective in men, namely use of aspirin and statins, do not afford a protective effect for coronary disease, cardiovascular mortality or all-cause mortality in women[2]. <1++>

MHT has the potential for improving the cardiovascular risk profile through its beneficial effects on vascular function, lipid levels and glucose metabolism; MHT has also been shown to reduce the incidence of new-onset diabetes mellitus[2]. <1+>

There is strong and consistent evidence that estrogen therapy may be cardioprotective if started around the time of menopause (often referred to as the 'window of opportunity' or 'timing' hypothesis)[3], and may be harmful if started more than 10 years after menopause[4]. <1+> In the 13-year follow-up of women in the WHI, the cumulative data in the 50–59-year-old age group showed a reduction of coronary heart disease (CHD) (HR 0.65; 95% CI 0.44–0.96.) The risk of myocardial infarction was also significantly decreased (HR 0.60; 95% CI 0.39–0.91)[5]. <1+> However, in this age group, the women receiving estrogen–progestogen (CE + MPA) in the WHI trial did not receive any overall CHD benefit (HR 1.27; 95% CI 0.93–1.74)[5]. Women <10 years since menopause who received CE + MPA showed a non-significant reduction in CHD (HR 0.90; 95% CI 0.56–1.45), suggesting a potential attenuation of the coronary benefit with this particular regimen using a continuous progestogen[5]. <1−>

Meta-analyses of RCTs, including data from the WHI, have shown a significant reduction in CHD as well as mortality in women treated with estrogen under the age of 60[6,7]. <1++> In the WHI, the cumulative results showed a reduction in all-cause mortality in the 50–59-year-old age group with estrogen alone and estrogen–progestogen, although the point estimates just missed statistical significance (RR 0.78; 95% CI 0.59–1.03 for estrogen; RR 0.88; 95% CI 0.70–1.11 for estrogen–progestogen)[5]. When mortality data for CE and CE + MPA from the two WHI trials were combined, the reduction in all-cause mortality was significantly reduced by 30%. Combining the data provided sufficient events to drive the data to significance[8]. <1+> Several meta-analyses have had similar findings[6,7,9,10]. In the most recent Cochrane analysis, women within 10 years of menopause had a reduction of all-cause mortality of 0.70 (95% CI 0.52–0.95) and of cardiovascular mortality of 0.52 (95% CI 0.29–0.96)[11]. <1+> An observational study from Finland recently reported that estradiol products (oral and transdermal) with and without progestogen decreased coronary and all-cause mortality significantly (12–54%)[12]; of note in this study, while longer duration of use decreased mortality, age of initiation did not make a difference[12]. <2++>

The three most recent prospective trials using MHT with coronary disease as the endpoint are DOPS[13], KEEPS[14] and ELITE[15].

The Danish Osteoporosis Prevention Study (DOPS) studied younger women at the onset of menopause who prospectively received standard doses of estradiol and norethisterone in an open-label fashion, or no treatment, for 10 years and had 16 years of follow-up[13]. There were significant reductions in mortality and in

hospitalizations for myocardial infarction and congestive heart failure. <1+>

The Kronos Early Estrogen Prevention Study (KEEPS) did not show a difference between CEE 0.45 mg, transdermal estradiol 0.05 mg and placebo in terms of intermediate endpoints: carotid artery intima-media thickness and coronary calcium[14]. These young healthy women had virtually no atherosclerosis and it is possible that there was insufficient progression over 4 years to detect differences between the groups. <1> The Early versus Late Intervention Trial with Estradiol (ELITE)[15] studied the effects of oral estradiol 1 mg and placebo in two groups of women, one <6 years from menopause and the other> 10 years from menopause, and showed a reduction in carotid artery intima-media thickness over time in the younger women, and no change in the older population, confirming that the 'timing' of estrogen treatment is important in influencing the progression of coronary disease[15]. <1+>

Initiation of MHT in elderly women (>60 years old) or those who are more than 10 years postmenopause may be associated with increased risk for coronary events. <1+> However, the cumulative 13-year data of the WHI and the recent Cochrane analysis did not show a significant increase in CHD or mortality in the older age groups <1−>; there was an increase in venous thrombosis and stroke with initiation of oral MHT in the older age groups[5,11]. <1+> Some data suggest that concomitant use of statins may mitigate the risk of venous thrombosis events following initiation of MHT in women over age 60[16]. <2++>

Key messages

- In women <60 years old, who are recently menopausal and with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy reduces CHD and all-cause mortality. [A]
- The daily continuous combined oral estrogen–progestogen data are less robust but other combined therapy regimens appear to be cardioprotective, as shown in the Danish and Finnish studies. [A]
- With cardiovascular disease being the leading cause of death in women, for women starting MHT <60 years of age and/or within 10 years of menopause, the most recent Cochrane analysis, other meta-analyses, and the WHI 13-year results all show a consistent reduction in all-cause mortality. [A]
- It is not recommended to initiate MHT beyond age 60 years solely for primary prevention of CHD. [A]

Stroke

The risk of ischemic stroke is related to age, but stroke is a rare event before age 60[1]. Stroke incidence may be increased when MHT is initiated in women >60 years of age, but is not associated with hemorrhagic stroke. <1+> Initiation of MHT in women <60 years of age and/or <10 years since menopause has no effect on the risk of stroke according to data from the 13-year follow-up data from the WHI and the Cochrane analysis[2,3]. <1+> The risk of ischemic stroke with MHT may be related solely to oral therapy, with lower doses having a smaller risk and no significant risk occurring with transdermal therapy[4], suggesting a primary thrombotic mechanism[5]. <2−>

Coagulation, venous thromboembolism disease and MHT

Venous thromboembolism events are the most prevalent adverse effect of oral estrogens in recently postmenopausal women. The MHT-related risk for serious venous thromboembolic events increases with age (although rare in low-risk women until age 60 years) and is also positively associated with obesity and thrombophilia. Epidemiological studies have not found any increased risk of VTE with use of transdermal estrogen. There is also strong evidence that the type of progestin associated with estrogen is of importance. Biological evidence supports all of these results. The use of transdermal estrogen associated with progesterone might be safer in regard to VTE, especially in women at high VTE risk.

The incidence of VTE (both deep vein thrombosis and pulmonary embolism) is estimated to be one to two cases per 1000 woman-years[1–3]. VTE strongly increases with age. Obesity, personal history of thrombosis (superficial or deep) and genetic thrombophilia are common VTE risk factors[1,4].

Venous thrombosis and oral estrogen with or without progestogen

Based on the results of RCTs and observational studies, the incidence of VTE is higher during the first year of oral estrogen use, with or without progestogen[5,6]. The initiation of MHT in older women and, to a lesser extent, the continued use of MHT are associated with an increased risk as compared to non-users. In the WHI, in the 50–59-year-old group, the excess risk of pulmonary embolism was six additional cases per 10 000 woman-years for estrogen–progestogen therapy, and four additional cases with estrogen

alone; both are far less than the risk of VTE in normal pregnancy[7]. <1+>

Whether the type of estrogen molecule is associated with different levels of venous risk remains controversial. In a recent population-based, case–control study of oral hormone therapy users, CEE use was associated with a higher risk of incident VTE than estradiol use[8]. These results need to be confirmed. <2>

Impact of progestogen with oral estrogen

The risk of a thromboembolic event may also be affected by the type and duration of progestogen. MPA may be associated with greater risk when used in oral therapy, as is the use of continuous combined regimens compared with sequential regimens. Moreover, the CEE arm of the WHI had a non-significant hazard ratio of VTE, especially in younger women[6,7]. <1−>

Venous thrombosis and transdermal estrogen with or without progestogen

Less than ten observational studies have assessed the risk of VTE associated with transdermal estrogen therapy[3]. Meta-analyses of these epidemiological studies have shown that transdermal estrogen did not increase the risk of VTE. The hazard ratio for VTE among users of transdermal therapy was close to one[9]. <2++>

Two observational studies underline the importance of the type of progestogen associated with estradiol[10–12]. Thus, these studies pointed to an increased risk of VTE in women using transdermal estrogen combined with norpregnane derivatives as compared to women using progesterone. <2+>

Venous thrombosis, route of administration and genetic markers

The combination of thrombogenic mutations and oral estrogen, especially CEE with or without progestogen, further enhanced the risk of VTE compared with women without mutations[2,3]. <1−>

In only one study, no significant difference was observed in risk of VTE between women with the factor V Leiden mutation or prothrombin G20210A mutation who used transdermal estrogen and those with a mutation who did not use estrogen[13]. <2+>

Venous thrombosis, route of administration and clinical risk factors

Obesity or personal history of VTE are major venous risk factors. The combination of oral estrogen use and an increased BMI resulted in a further increase in the VTE[2,3]. <1+>

In one study, however, current use of transdermal estrogen did not confer an additional risk on women who were overweight or obese[14]. <2>

Moreover, only one retrospective cohort study has assessed the impact of MHT by route of estrogen administration on the risk of recurrent VTE[15]. Oral but not transdermal estrogens are associated with a higher risk of recurrent VTE among postmenopausal women. This result needs to be confirmed by larger studies. <2>

Coagulation plausibility

Biological evidence supports the observation of an increased VTE risk among users of oral estrogen therapy and a neutral impact among users of transdermal estrogen therapy. Orally administered estrogen (estradiol or CEE) may exert a prothrombotic effect through the hepatic impact of these molecules[16–20]. The prothrombotic effect is possibly related to high concentrations of estrogen in the liver due to the 'first-pass' effect. Randomized trials that compared oral and transdermal estradiol therapy have demonstrated that transdermally administered estrogen has no or little effect in elevating prothrombotic factors and may have beneficial effects on proinflammatory markers. <1++>

Recommendations and key messages

- Oral estrogen therapy is contraindicated in women with personal history of VTE. [A]
- Transdermal estrogen therapy should be the first choice in obese women suffering from climacteric symptoms. [B]
- The risk of venous thrombosis increases with age and in the presence of other risk factors, including congenital or acquired thrombophilic disorders. ☑
- A careful assessment of personal and family history of VTE is essential before prescribing hormone therapy. ☑
- The risk of venous thromboembolic events increases with oral MHT but the absolute risk is rare below age 60 years. ☑
- Observational studies point to a lower risk with low-dose transdermal therapy associated with progesterone, underlined by a strong biological plausibility. ☑
- Some progestogens, e.g. MPA, norpregnane derivatives and continuous combined regimens,

may be associated with greater risk of VTE in oral MHT users. [C]
- The incidence of VTE is less frequent among Asian women. [C]
- Population screening for thrombophilia is not indicated prior to MHT use. [C]
- Selective screening may be indicated on the basis of personal and familial history. [D]

Central nervous system

Purpose and scope

This section of the guideline reviews evidence on effects of MHT and related compounds on cognition, mood, and other neurological disorders. MHT use during midlife is of particular interest, as MHT is most likely to be initiated and used during the menopausal transition and early postmenopause. Moreover, some health-related outcomes may differ for midlife MHT use compared to MHT use later in the postmenopause. For cognition, we sought evidence regarding cognitive change in women without cognitive impairment (cognitive aging), cognitive change in women with Alzheimer's disease, and risks of developing Alzheimer's disease or another form of dementia. For mood, we examined outcomes in midlife women with and without depression. For epilepsy, migraine headache, multiple sclerosis, and Parkinson's disease, we sought evidence on associations of MHT with disease risk and symptoms.

Does MHT initiated and used during midlife affect cognitive aging?

Forgetfulness, trouble concentrating, and other cognitive symptoms are common during midlife. During the menopausal transition, many women experience transient cognitive impairment, which is usually of small magnitude[1]. There is likely no persisting effect of the natural menopause on memory or other cognitive functions[2]. <2+ to 3>

A large, long-duration, three-arm trial of MHT in women below age 60 years showed no cognitive benefit or harm after mean treatment periods of 2.85 years (CEE 0.45 mg/day or transdermal estradiol 0.05 mg/day, with cyclical oral progesterone, versus placebo)[3]. <1++> In follow-up analyses from the WHI approximately 7 years after trial termination, there was no residual cognitive effect of CEE 0.625 mg/day, with or without continuous MPA, begun at age 50–55 years[4]. <1+>

Surgical menopause is distinguished from natural menopause by social and demographic features. Moreover, the transition is abrupt, occurs at an earlier age, and involves the loss of androgens as well as estrogens and progesterone[5]. Results from small, short-duration clinical trials in surgically menopausal women suggest that estrogen therapy could be of short-term cognitive benefit when initiated at the time of oophorectomy[5]. <1−>

Does MHT initiated after midlife affect cognitive aging?

MHT has been assessed in four large, long-duration trials in healthy postmenopausal women aged 60 + years[6–9]. Overall findings indicated no significant cognitive benefit or harm after mean follow-ups of 3 years (CEE 0.625 mg/day and continuous MPA, women with a uterus)[6], 3 years (CEE 0.625 mg/day, women without a uterus)[7], 3 years (CEE 0.625 mg/day with or without continuous MPA)[9], or 2 years (transdermal estradiol 0.014 mg/day)[8].

Does MHT affect cognitive symptoms of women with Alzheimer's disease or dementia?

For Alzheimer's disease, older women without a uterus were assessed in a large, long-duration trial[10] (unopposed CEE 0.625 or 1.25 mg/day, or placebo). Findings were null, and results from most small, short-duration trials similarly suggest no important effect of MHT on cognitive outcomes[11]. <1+>

Does midlife MHT affect the risk of dementia?

Older systematic reviews of case–control and cohort studies suggest risk reductions associated with MHT use of about 34–44%[12,13]. Risk reductions are similar in observational studies where hormone exposure was assessed prior to dementia onset[11], reducing the likelihood of recall bias. <2+>

Does MHT initiated after midlife affect the risk of dementia?

Two large, long-duration ancillary studies from the WHI examined MHT (unopposed CEE 0.625 mg/day, women without a uterus; CEE 0.625 mg/day combined with MPA, women with a uterus) with outcomes of all-cause dementia. The number of events was small (108 dementia cases in the two trials combined), and Alzheimer's disease was not examined separately. For unopposed estrogen therapy, the hazard ratio (HR) was not significantly different from 1; for combined therapy, it was increased. In an analysis that combined both

hormone groups, the HR for MHT use was significantly elevated (HR 1.8, 95% CI 1.2–2.6)[14]. <1+>

Trial participants were 65–79 years old. Dementia attributed to combined MHT was uncommon in this age group, about 2.3 cases per 1000 woman-years of use. For unopposed estrogens, the point estimate of attributable risk was less, 1.2 per 1000 woman-years of use. Extrapolating these risk estimates to healthy women aged 50–59 years – an age group not studied in these trials – implies that dementia risk attributable to MHT would be rare among younger postmenopausal women, about 0.2 additional cases per 1000 woman-years.

Risk of Alzheimer's disease and dementia – effect of age

Discrepant findings on dementia risk from observational studies of midlife MHT use and the WHI clinical trials could reflect unrecognized confounding in observational studies, failure of findings in older postmenopausal women to generalize to younger postmenopausal women, or both[15]. Three observational studies explored possible differences based on timing. One found reduced Alzheimer risk for MHT use among younger, but not older, postmenopausal women[16]. Another described reduced dementia risk for MHT used during midlife and not during old age, contrasted with increased dementia risk for MHT used during old age but not during midlife[17]. The third reported reduced Alzheimer risk for MHT initiated within 5 years of menopause but no effect on risk for MHT initiated more than 5 years after menopause[18]. These observational findings support the critical window, or timing, hypothesis of MHT for Alzheimer risk[15]. <2+>

What are the cognitive effects of other estrogenic compounds?

The SERM raloxifene is approved for the treatment of osteoporosis in postmenopausal women. In a large, long-duration trial of raloxifene in postmenopausal women with osteoporosis, raloxifene (60 and 120 mg/day) had no effect on most neuropsychological measures[19]. High-dose (120 mg/day) but not standard dose (60 mg/day) raloxifene reduced risk of mild cognitive impairment (RR 0.67; 95% CI 0.46–0.98)[20]. <1+> High-dose raloxifene does not significantly affect cognition in women with Alzheimer's disease, although clinical trial results do not exclude the possibility of small cognitive effects[21]. <1+>

Two large, long-duration trials examined cognitive effects of soy isoflavone supplements in healthy postmenopausal women. A study of older postmenopausal women identified no significant effect on neuropsychological performance after 12 months[22]. Another study, which included both younger and older postmenopausal women, found no effect on individual neuropsychological measures or a global composite derived from all measures after 2.5 years; effects were similar in younger and older women[23]. Visual memory improved significantly among women assigned to the isoflavone group compared to the placebo group, but performances on other cognitive factors did not differ[23]. <1++>

What are the effects of MHT on midlife depressive symptoms and depression?

The incidence of major depression is probably similar in old age compared to younger age groups[24], but depression and depressive symptoms are more common during the menopausal transition and early postmenopause than shortly before the menopause[1]. <2+ to 2−>

Findings are inconsistent as to whether MHT improves or has no effect on depressive symptoms in younger postmenopausal women without depression. A large 4-year study reported that CEE (0.45 mg/day, with cyclic progesterone) but not transdermal estradiol (0.05 mg/day, with cyclic progesterone) improved depressive symptoms compared to placebo[3]. A large 4-month trial found no effect on affect for CEE (0.625 mg/day, with continuous MPA)[25]. <1++>

Two small, short-duration clinical trials assessed MHT in women with depression or depressive symptoms during the menopausal transition. After 3 weeks, depression scores improved significantly in depressed women treated with transdermal estradiol (0.05 mg/day) compared to placebo[26]. After 12 weeks, depressive disorders were significantly more likely to remit with transdermal estradiol (0.1 mg/day) compared to placebo[27]. <1−>

What are the effects of MHT on other neurological disorders?

Hormone exposures are of potential relevance to a number of neurological disorders. Estrogens have been linked to migraine headache[28], and headache prevalence is lower after menopause than before[29]. There are no clinical trial data on MHT and headache symptoms or frequency. Multiple sclerosis symptoms are widely believed to be influenced by hormonal status, but relevant clinical trials are not yet reported[30]. For Parkinson's disease, observational studies suggest no consistent association between MHT use and Parkinson risk[31]. A small, under-powered, 8-week pilot trial (CEE

0.625 mg/day) in postmenopausal women with advanced Parkinson's disease showed no significant effect of MHT on study outcomes[32]. For some women of reproductive age with epilepsy, seizure frequency varies in association with the menstrual cycle. A small, 3-month clinical trial in midlife postmenopausal women with epilepsy reported that CEE (0.625 mg/day or 1.25 mg/day, combined with MPA) led to a dose-related increase in seizure frequency[33]. <1− to 2−>

Key messages

Cognitive aging

- MHT should not be used to enhance cognitive function. [A]
- Healthy women considering MHT for approved indications need not be overly concerned that MHT will adversely affect cognitive function. [A]
- Estrogen therapy may be of short-term cognitive benefit to surgically menopausal women when initiated at the time of oophorectomy. [B]
- Phytoestrogen (soy isoflavone) supplements used by healthy postmenopausal women in a daily dose comparable to that consumed in traditional Asian diets have no overall effect on cognition. [A]

Alzheimer's disease and dementia

- For women with Alzheimer's disease, MHT initiated after the onset of dementia symptoms does not benefit cognitive function or slow disease progression. [A]
- MHT initiated and used after midlife increases risk of dementia. [A]
- MHT initiated during midlife is associated with reduced risk of Alzheimer's disease and dementia. [B]
- Extrapolated from risks in older postmenopausal women, estimates in women younger than 60 years imply that dementia risk attributable to MHT would be rare in this age range. [D]

Depressive symptoms and depression

- Findings are inconsistent as to whether MHT improves or has no effect on depressive symptoms in younger postmenopausal women without depression. [A]
- For depression or depressive disorders that occur during the menopausal transition, short-term estrogen therapy may improve affective symptoms or increase the likelihood of remission. [B]

Other neurological disorders

- MHT may increase seizure frequency in women with epilepsy. [B]
- MHT is not associated with Parkinson's disease risk. [B]
- Effects of MHT on symptoms of migraine headache, multiple sclerosis, and Parkinson's disease are largely unknown. [B]

Breast cancer

The incidence of breast cancer varies in different countries. Therefore, currently available data may not be applicable everywhere. The degree of association between breast cancer and MHT remains controversial. Most long-term studies reflect the use of one specific combination of oral estrogen and progestogen and suggest a possible increased risk with increasing duration. The WHI estrogen + progestogen trial and several large observational studies reported an increased risk after at least 5 years of use, suggesting a possible promoter effect on existing tumors[1–7]. Only the unadjusted relative risk was significant and, when adjusted on risk factors, the significance was no longer reached[2]. <1+> Combined MHT can increase breast density, which complicates screening and increases mammography frequency[1]. <1+>

The possible increased risk of breast cancer associated with MHT is small and estimated at less than 0.1% per annum, or an incidence of < 1.0 per 1000 women per year of use. <1+> It is similar or lower than the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption. <2++> Data from the WHI study demonstrated no increased risk in first-time users of MHT during the 5–7 years since initiation of treatment[2]. <1+> The WHI study also demonstrated that 7.1 years of treatment with unopposed CEE decreased the risk of breast cancer diagnosis and mortality in hysterectomized women[8]. <1+>

However, the majority of subjects in the WHI study were overweight or obese, which may have affected their basal breast cancer risk. The estrogens used were conjugated estrogens and not estradiol. This cannot reliably be extrapolated to younger and less obese women and to estradiol. <4>

There is no randomized head-to-head study between estrogen alone and combined MHT but several observational studies including the Nurses' Health Study suggest that long-term administration of unopposed estrogens alone can be associated with a small increase in the relative risk of breast cancer in leaner, younger

women, but that potential risk is lower than that associated with combined treatment[5,6,9]. <2++>

Tibolone does not appear to be associated with an adverse effect on mammographic density[10]. The risk of breast cancer with tibolone is not fully evaluated in normal women but tibolone increases the rate of recurrence in breast cancer survivors[11]. <1+>

Three studies suggest that micronized progesterone or dydrogesterone could be associated with a lower risk than synthetic progestogen. A large European observational study suggested that micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens[6]. <2+> A case–control study from France also showed a lower level of risk with progesterone than synthetic progestogens[12]. <2−> A registry study from Finland reported no increase in risk with dydrogesterone after at least 5 years of use compared to synthetic progestogens, which were associated with a small increase in risk[13]. <2+> Currently available data imply no difference in risk between oral and transdermal routes of estradiol administration[4]. <2+> However, there are not enough data from adequately powered clinical studies to fully evaluate possible differences in the incidence of breast cancer using different types, doses and routes of estrogen, type of progestogens and androgen administration.

Key messages

- The risk of breast cancer in women over 50 years associated with MHT is a complex issue.
- The increased risk of breast cancer is primarily associated with the addition of a synthetic progestogen to estrogen therapy (CEE + MPA continuous combined therapy) and related to the duration of use. [B]
- The risk may be lower with micronized progesterone or dydrogesterone than with a synthetic progestogen. [C]
- The risk of breast cancer attributable to MHT is small and the risk decreases progressively after treatment is stopped. [B]
- There is a lack of safety data supporting the use of MHT (estrogen therapy or estrogen–progestogen therapy) in breast cancer survivors.
- Breast cancer risk should be evaluated before MHT prescription. [D]
- The possible greater risk of breast cancer observed with MHT may be partially decreased by selecting women with a lower individual baseline risk, including low breast density, and by providing education about preventive lifestyle measures (reducing body weight, alcohol intake and increasing physical activity). [D]
- Annual mammograms should be proposed in case of high breast density in women using MHT. [D]

Endometrial safety and bleeding

Virtually all health-care providers are aware of the fact that postmenopausal bleeding is 'endometrial cancer' until proven otherwise, although only 1–14% of such patients will actually prove to have endometrial cancer[1]. <1+> Endometrial evaluation in any postmenopausal patient with bleeding, whether on no medication, MHT, or a SERM, requires evaluation. The evaluation of bleeding has undergone a transformation in the past few years with the recognition that endometrial pathologies are not always global and, thus, blind endometrial biopsies, when negative, are not nearly as significant or reliable as when positive[2]. Blind sampling is still an appropriate first step in evaluation. However, if not positive for cancer or atypical complex hyperplasia, techniques like saline infusion sonohysterography or hysteroscopy, preferably in an office setting, are necessary to triage global versus focal processes[2]. Blind endometrial sampling has been shown to be very effective if a cancer occupies more than 50% of the surface area of the endometrium[3]. <2++>

In terms of MHT, the association of unopposed estrogen therapy with endometrial hyperplasia/neoplasia is well known[4]. <1+> The risk associated with unopposed estrogen therapy is dependent on dose and duration of treatment[5]. <2++> The addition of a progestogen, in either continuous combined or cyclical fashion, has been shown to reduce the risk of endometrial neoplasia associated with estrogen therapy[6]. <1++> Inhibiting progression of estrogen-induced proliferation to hyperplasia will depend on the dose and duration of progestogen used. Unopposed estrogen for 1 year yielded a 20% incidence of hyperplasia[7]. <1+> Cyclic progestogen given for more than 10 days monthly reduces this rate to that seen with placebo[6], whereas continuous combined MHT is rarely associated with endometrial hyperplasia. <1++> In the WHI, which employed continuous combined MHT, there was a statistically non-significant 19% decline in endometrial hyperplasia compared to placebo[8]. <1+>

Adequate endometrial protection was demonstrated in MHT users with sequential and continuous micronized progesterone in the PEPI trial[7]. <1+> However, in the EPIC prospective cohort study, more endometrial cancers occurred in sequential combined estradiol/micronized progesterone MHT users: HR 2.42 (95% CI

1.53–3.83)[9]. <2++> A possible explanation is that there was reduced compliance in estradiol/micronized progesterone users because there were two separate components to their MHT.

The levonorgestrel-releasing intrauterine system (IUS) has been reported to be more effective than sequential MPA but comparable to other systemic progestogen regimens for endometrial protection in perimenopausal and postmenopausal women taking estrogen therapy[10]. <1+>

More recently, a regimen combining the SERM, bazedoxifene, with CEE has been introduced as a progestogen-free alternative for MHT in women with a uterus[11]. <1+> Attempts to combine other SERMs with estrogens resulted in an unacceptably high incidence of endometrial hyperplasia[12]. <1+>

Because the addition of progestogen, especially sequentially, may produce unwanted side-effects, there have been attempts to prescribe 'long-cycle' progestogen supplementation with mixed results, but these used different regimens. In one study that compared long-cycle (12 weeks) with traditional (4 weeks) supplementation, there was an increase in neoplasia[13]. <2+> Another attempt, simply comparing patient outcomes to 'acceptable rates of hyperplasia' as defined by regulatory agencies, found long-cycle use (12 weeks) to be appropriate[14]. <2−>

Tibolone is also used extensively as a form of MHT. It is not, however, available world-wide. A large epidemiological study showed a statistically significant, almost three-fold increase in endometrial cancer compared to never-users of MHT over a mean follow-up of 9 years[15]. <2+> However, other studies have found that tibolone does not induce endometrial hyperplasia or carcinoma in postmenopausal women and was associated with a better vaginal bleeding profile than CEE + MPA in a continuous combined fashion[16]. <1+>

The use of SERMs, although not strictly a form of MHT, is increasing. Thus, they deserve mention here. Tamoxifen, the first real SERM, has a small but definite association with endometrial neoplasia[17]. <1+> As a result, virtually every other SERM has undergone clinical programs to evaluate uterine safety. Raloxifene and bazedoxifene, used in low to medium dose, have a similar effect on the postmenopausal endometrium as placebo[18,19]. <1+> In higher doses (30–40 mg daily), bazedoxifene appears to reduce endometrial thickness. Ospemifene, approved for oral treatment of vulvovaginal atrophy/genitourinary syndrome of menopause, has demonstrated endometrial safety[20,21]. <1+> Lasofoxifene, approved in the European Union but not the United States and never commercially developed, had proven endometrial safety through a 5-year randomized, placebo-controlled osteoporosis study[22]. <1+>

Key messages

- Postmenopausal bleeding is 'endometrial cancer until proven otherwise', although only 1–14% of such patients will actually have cancer. [A]
- Blind endometrial sampling is appropriate for initial evaluation but is only reliable when endometrial cancer exceeds more than 50% of the endometrial surface area. [B]
- Adequate doses of micronized progesterone appear to be 200 mg per day for 10–14 days in sequential therapy and 100 mg per day for continuous combined therapy where the estradiol dose is 2 mg/50 μg or less. [B]
- Higher doses of progesterone may be required for endometrial protection when higher doses of estradiol are used, or in women with high BMI. ☑
- Unopposed estrogen therapy is associated with a duration and dose-related increase in risk of endometrial hyperplasia and cancer. [A]
- Endometrial protection requires an adequate dose and duration of progestogen. [A]

Ovarian cancer

The IMS recommendations of 2013 stated that 'Long-term, estrogen-only therapy may be associated with a small attributable risk of ovarian cancer of 0.7 per 1000 women per 5 years of use, whilst either a smaller, or no, increased risk is seen with combined E + P therapy'[1].

A meta-analysis of 52 studies, principally focused on 17 follow-up studies, has since been published, in which it has been claimed that MHT (both estrogen-only and E + P) increases the risk of ovarian cancer by some 1.2–1.4-fold, both overall, and even when currently used, or last used less than 5 years previously, and even when such use lasted less than 5 years[2]. <2++> The increased risks were confined to serous and endometrioid tumors. The attributable risk for 5 years of use at age 50 years was given as one extra case per 1000 users, and one extra death per 1700 users.

It has further been claimed that the increased risk 'may well be largely or wholly causal', and that claim has attracted considerable publicity. However, the validity of the evidence has been challenged, for the following reasons:

- The likelihood that symptoms of as yet undiagnosed ovarian cancer (e.g. dyspareunia, urinary symptoms) were attributed to the menopause, and resulted in the use of MHT;

- That is: ovarian cancer 'caused' current or recent short-duration MHT use, not the reverse;
- The likelihood that MHT-exposed cases were less commonly lost to follow-up than exposed non-cases;
- The inclusion in the meta-analysis of an unknown number of oophorectomized women who were not at risk;
- Absence of information on history of hysterectomy for 66% of the women;
- Unreliable classification of histological subtypes of ovarian cancer;
- Low-magnitude associations, for which it was impossible to discriminate between bias and causation;
- Failure to evaluate dose–response;
- Absence of a duration–response effect;
- Discordant findings among the 52 studies;
- Absence of experimental evidence to suggest that MHT induces ovarian carcinogenesis.

The published risk estimate calculations have been challenged. In a commentary on ovarian cancer and MHT, Gompel and Burger calculate that, for women aged 50–54 years, the absolute risk is about 1 per 10 000 women per year of use, with a base rate of 1.2 per 1000 per 5 years and an absolute excess of 0.55 per 1000 per 5 years[3]. Further good-quality data are needed to allow definitive statements about ovarian cancer risk.

Key message

- Based on the evidence to date, the association between MHT use and ovarian cancer remains unclear.

Lung cancer

Lung cancer incidence ranks second in the list of female cancers, but it has surpassed breast cancer as the leading cause of cancer death among females in more developed countries[1,2]. Advanced age and smoking are the main risk factors. <2++> A large, prospective, observational study from China suggested that lung cancer incidence might be higher in women who had gone through menopause at baseline compared to women of the same age who were still menstruating[3]. <2+> A case–control study from Italy found that age at menopause above 51 years was associated with reduced risk for lung cancer (odds ratio (OR) 0.49; 95% CI 0.31–0.79) and that the use of MHT had a favorable outcome as well (OR 0.63; 95% CI 0.42–0.95 vs. never users)[4]. <2−> The risk did not substantially change among women with longer duration of MHT. A meta-analysis of 18 various types of studies (RCTs, case–control, cohort, cancer registry) showed an overall benefit for ever use of MHT (RR 0.80, 95% CI 0.72–0.89)[5]. <2++> However, the reduction in risk was seen in estrogen-only users, whereas there was no significant effect associated with combined E + P use. The authors noted that significances were found in analyses only when smoking and non-smoking women, various hormone regimens, or histological subtypes, respectively, were pooled. A large-scale, observational, prospective study from California reached a conclusion that there was no association between intake of MHT and lung cancer risk after adjustments for smoking, histology of the tumor, type of menopause and of the hormone preparation[6]. <2+> The WHI clinical trials actually had the same conclusions[7,8]: HR 1.17, 95% CI 0.81–1.69 in the estrogen-alone arm; HR 1.23, 95% CI 0.92–1.63 in the E + P arm, but more women died from lung cancer in the combined MHT group than in the placebo group (HR 1.71, 95% CI 1.16–2.52). <1+> Further analyses from the WHI study, whether an overview of findings from the two WHI clinical trials with extended post-intervention follow-up[9], or a joint analysis of the WHI observational study data and the clinical trial data[10] reached similar conclusions of no overall effect. Two subgroups in the latter study did show significant associations: for all lung cancers, women with previous use of E + P of < 5 years were at reduced risk (HR 0.84; 95% CI 0.72–0.98), and a similar risk reduction for non-small cell lung cancer was recorded for 5 to < 10 years of any previous hormone use (HR 0.84; 95% CI 0.71–0.99). Later age at menopause was associated with risk reduction as well. <1+> To summarize, data on MHT and lung cancer are inconsistent and do not point at a clear association of MHT in the pathogenesis or outcome of pulmonary malignancies.

Key messages

- Neither of the two WHI clinical trials (estrogen-alone or E + P) demonstrated a significant increase in lung cancer incidence among hormone users compared to placebo. [A]
- In the WHI E + P clinical trial, the risk of death from lung cancer was higher. However, there was no effect on mortality in the 50–59-year-old women. [A]
- Combining data from the WHI clinical and observational studies allowed identification of subgroups in which MHT proved protective: for all lung cancers – previous use of E + P for less than 5 years; for non-small cell lung cancer – previous use of any MHT for 5–10 years. [B]

- Smoking is an important risk factor in this context as well: in the combined WHI clinical plus observational study analysis, current smokers had increased risk associated with 10 or more years of E + P use. [B]

Colorectal cancer

Colorectal cancer is one of the leading types of cancer in women. Its incidence varies in different world regions, with an age-adjusted range between 3 and 33 per 100 000 women[1]. <2+> Incidence strongly increases with age; median age at diagnosis is about 70 years in developed countries. Many risk factors may have an impact (family history, smoking, obesity, diet and lifestyle, etc.), but MHT is mentioned in this context as well. The Nurses' Health Study, a very large prospective, observational study from the USA, found that the RR of colorectal cancer in current hormone users was 0.65 (95% CI 0.50–0.83)[2]. <2++> In a meta-analysis of 18 epidemiologic studies of MHT and colorectal cancer, the same group reported on a 20% reduction (RR 0.80, 95% CI 0.74–0.86) in risk of colon cancer and a 19% decrease (RR 0.81, 95% CI 0.72–0.92) in the risk of rectal cancer for postmenopausal women who had ever taken hormone therapy compared with women who never used hormones[3]. <2++> Both the WHI clinical trials (randomized, placebo-controlled) provided data on colon cancer and MHT which were not in line with the previous observational studies. On the one hand, the E + P study in women with a uterus did show a benefit, with RR = 0.63 (95% CI 0.43–0.92) for the hormone users[4], but, on the other hand, there was no significant effect of estrogen-alone on the incidence of colorectal cancer in hysterectomized women (RR 1.08; 95% CI 0.75–1.55)[5]. <1+> The reduced risk in the E + P study was predominantly for local disease and, where spread had occurred, there was more node involvement and a more advanced stage at diagnosis amongst users of MHT. Further data from the WHI projects were published in later years, either combining the results from the clinical and the observational trials[6], or combining the clinical trials with some additional years of follow-up post-stopping of therapy[7]; they were summarized as yielding an insignificant effect or having no important clinical effect. It should be noted that all US studies actually used one specific hormonal medication, namely CEE and MPA. In a large, observational study from France, where most women take estradiol and non-MPA progestogens, ever-use of MHT (all types and routes) was not associated with risk for adenoma or cancer, but ever-use of estrogen-alone was associated with increased risk for adenoma (HR 1.22, 95% CI 1.05–1.41), whereas a decreased risk of cancer (HR 0.72; 95% CI 0.56–0.94) was reported[8]. <2++> Tibolone is another type of non-estrogenic MHT, which is often prescribed in Europe. A randomized, placebo-controlled study on osteoporotic women gave encouraging results concerning the risk of colon cancer, with a relative hazard 0.31 (95% CI 0.10–0.96)[9]. <1+> In conclusion, on the whole there seems to be a beneficial impact of MHT on colon cancer risk, but data are inconsistent with regard to estrogen-alone treatment. MHT should not be used solely for the prevention of colorectal cancer.

Key messages

- The majority of observational studies show a reduced risk of colorectal cancer amongst users of oral MHT. [B]
- Three meta-analyses have reported a reduced risk of colorectal cancer with MHT use with benefit persisting for 4 years after cessation of therapy. [A]
- Results from the WHI randomized trial of estrogen-only therapy showed no effect of estrogen-only therapy on risk of colorectal cancer. [A]
- In the WHI RCT of E + P therapy, colorectal cancer risk was reduced (RR 0.56; 95% CI 0.38–0.81). This effect was predominantly for local disease and, where spread had occurred, there was more node involvement and a more advanced stage at diagnosis amongst users of MHT. [A]
- To date, there are limited data for an effect of non-oral MHT on risk of colorectal cancer.
- The Long-term Intervention on Fractures with Tibolone (LIFT) study demonstrated that tibolone was associated with a reduced risk of colon cancer in women aged 60–79 years. [A]
- MHT should not be used solely for the prevention of colorectal cancer. [D]

Cervical cancer

Cervical cancer is the fourth most common cancer world-wide for females, and the seventh most common cancer overall, with more than 527 000 new cases diagnosed in 2012 (8% of female cases and 4% of the total). Incidence rates of cervical cancer are highest in Eastern Africa and lowest in Western Asia, Australia, New Zealand and North America[1]. <2++> The peak age for developing cervical cancer is 30–35 years in western countries and declines steadily after this until a second peak in incidence in very old age. National screening programs in many developed countries have led to a

significant decrease in incidence rates and, in particular, the incidence in women aged over 45 years has declined significantly since the mid-1970s[1].

The uterine cervix is a part of the female reproductive tract that is highly responsive to estrogen. <1++> However, the role of estrogen in cervical cancer, which is strongly associated with HPV infections, until now is poorly understood.

Investigating the correlation between MHT and cervical cancer risk has been hampered to a much greater extent than the assessment of hormonal contraceptives by two main problems: first, the predominant use of MHT is in rich countries where cervical cancer risk has been greatly reduced by cytological screening, and, second, there is the additional tendency of MHT users to be screened more intensively than non-users. Long-term cohort studies have shown no increased risk of cervical cancer with MHT use[2]. <2++> The only relatively unbiased data on MHT and cervical cancer and precancerous lesions derive, therefore, from the two randomized, placebo-controlled studies, the WHI and the Heart and Estrogen/progestin Replacement Study (HERS). <1+> In the WHI (combined arm) with cytological findings assessed during a 6-year follow-up period, the annual incidence rate of any cytological abnormality in the MHT group was significantly higher than in the placebo group (HR 1.4; 95% CI 1.2–1.6), but no difference was found in incidence rates of high-grade squamous intraepithelial lesions, which would be comparable to cervical intraepithelial neoplasia 2/3 and cervical cancer[3]. A non-significantly higher incidence of cytological abnormalities (HR 1.4; 95% CI 0.9–2.0) was reported among women in the MHT group in HERS but, like the WHI, the risk of cervical cancer was not increased[4].

Any association between MHT use and adenocarcinoma of the cervix is unclear. Recently, a retrospective Finnish registry study investigating postmenopausal women ($n = 243\,857$) using 5 years MHT found an increased risk of adenocarcinomas (SIR (standardized incidence ratio) 1.83; 95% CI 1.24–2.59), whereas the risk for squamous cell carcinoma decreased (SIR 0.34; 95% CI 0.16–0.65)[5]. <2+> Further studies are needed in this area of research.

Key messages

- In the WHI randomized, controlled trials and in HERS, there was no increase in risk of cervical cancer with MHT use. [A]
- Long-term cohort studies have shown no increased risk of cervical cancer with MHT use. [B]

Upper gastrointestinal tract cancers

Hepatocellular cancer

Hepatocellular carcinoma (HCC) is an uncommon malignancy and few studies have looked into any associations with MHT. Examination of data from a framework of case–control studies conducted in Italy revealed an OR of 0.2 (95% CI 0.1–0.8) for ever-users ($n = 3$) compared with never-users (hospital-based controls, $n = 102$)[1]. <2+> However, a recent study with pooled data from 11 cohorts in the US assessing 800 000 women found no effect of MHT as a whole or when analyzed by age at natural menopause, past or current use, type of hormone and duration of exposure[2]. <2+> The investigators did discover, however, that bilateral oophorectomy was associated with a significantly increased risk of HCC (HR 2.67; 95% CI 1.22–5.85). They suggested that the previous positive associations would disappear if proper adjustments for oophorectomy had been done.

Key messages

- There is no clear association between MHT use and HCC. [C]
- Bilateral oophorectomy may be associated with an increased risk of HCC. [C]

Gastric, esophageal and gallbladder cancers

In an observational, prospective study from Shanghai, China, only 2.1% of person-years were related to postmenopausal women who were exposed to MHT, and the incidence of gastric cancer among this subgroup was similar to that in never-users[3]. <2+> Interestingly, the study also found that increasing time since menopause and shorter years of fertility were associated with an increased risk of gastric cancer. This would be in line with previous studies, which demonstrated a protective effect of MHT in populations with higher rates of hormone use. A nested case–control study from the UK showed that current use of MHT was associated with a reduced risk of gastric cancer (OR 0.56; 95% CI 0.33–0.96) as well as past use (OR 0.25; 95% CI 0.09–0.70)[4]. <2−> In fact, a meta-analysis of seven observational studies (cohort and case–control) pointed to the same association[5]: comparing ever-users with never-users of MHT demonstrated a significant reduction in gastric cancer risk (RR 0.77; 95% CI 0.64–0.92). <2++>

Although gender differences in susceptibility for esophageal cancer suggest a role for estrogen, there have been relatively few studies that examine possible links with MHT. Lindblad and colleagues' database

included 299 patients with esophageal cancer, in whom no association between the tumor risk and MHT was detected (OR 1.17; 95% CI 0.41–3.32)[4]. <2−> Yet a meta-analysis of eight cohort studies of various types showed a beneficial effect with a 28% reduction in pooled risk in the hormone users (RR 0.72; 95% CI 0.60–0.86)[6]. <2++>

While it is well established that the rate of gallbladder disease may be even 50% higher among women on oral MHT, reports on an association with gallbladder cancer are lacking. A single study from Italy pointed to increased risk for those who had ever used MHT (OR 3.2; 95% CI 1.1–9.3) and the ratio tended to rise with longer duration[7]. <2−>

Key messages

- There are few good studies examining links between upper gastrointestinal tract cancers, menopause and MHT use.
- MHT use may be associated with a reduced risk of gastric cancer. [C]

General and sexual quality of life in the menopause

Healthy aging is highly relevant to general quality of life and sexual well-being and sexuality is still important to many elderly women across the menopause and beyond[1]. Menopausal symptoms are strongly related to quality of life when using validated and appropriate condition-specific instruments[2]. <1+> Both age and declining levels of sex hormones have detrimental effects on sexual functioning, with a significant increase in vaginal dryness/dyspareunia and a significant decrease in desire and sexual responsiveness[3–6]. <2++> Surgical menopause is more likely to be associated with sexual dysfunction, especially hypoactive sexual desire disorder, due to the more profound endocrine deprivation[7]. <2++> Psychological and socio-relational factors are very important, influencing the clinical relevance of sexual symptoms and the level of distress in postmenopausal women. <2++> Special attention should be paid to women with natural menopause at a younger age, because the burden of premature menopause encompasses several biopsycho-social aspects influencing quality of life and sexual well-being, including the grief of infertility in some cases[8]. <2+> Iatrogenic menopause in breast cancer survivors and in women with other malignancies is highly disruptive in the context of quality of life and sexual well-being, an issue that should be further investigated in light of the emerging reality of cancer survivors[9]. <2+>

It is mandatory to include appropriate questions to investigate sexual well-being, because women may not be willing to initiate a conversation on sexual interest, behavior and activity themselves, but they usually appreciate being questioned by doctors. Validated tools (self-administered questionnaires/daily diaries and event logs/semi-structured interviews) may be used properly to diagnose female sexual dysfunction (FSD) and to gain information on sexual constructs and relationships, taking into account the biopsychosocial model[10]. <2++>

Determination of circulating sex steroids is not routinely helpful and a diagnosis of androgen deficiency in healthy women should not be primarily based on measurements of androgens because their correlation with specific signs and symptoms is currently inconsistent[11]. <1+>

The pivotal role of vulvovaginal atrophy (VVA) (referred to as genitourinary syndrome of menopause by NAMS/International Society for the Study of Women's Sexual Health, ISSWSH) should be always considered because the two most common symptoms, vaginal dryness and dyspareunia, may induce significant changes in other domains of sexual response (desire, arousal, orgasm satisfaction), as well as pelvic floor dysfunction[12–14]. <2++>

The multidimensional nature of women's sexuality has limited the possibility to establish a clear effect of MHT on FSD. However, MHT with estrogens alone or in combination with progestogens is associated with a small to moderate improvement in sexual function, particularly in pain, when used in women with menopausal symptoms or in early postmenopause (within 5 years of amenorrhea)[15–19]. <1+> Tibolone, a synthetic steroid classified as a selective tissue estrogenic activity regulator, is of value in treating postmenopausal women with FSD[20]. <1+> Hormonal and non-hormonal treatments and/or psychosexual strategies should be individualized and tailored according to a woman's history and current needs, taking into account also the partner's availability, general and sexual health of the partner and quality of the intimate relationship[15]. <2++>

Key messages

- Consider age, type and time since menopause, vasomotor and mood symptoms, general health, including medications for chronic conditions, as well as intrapersonal and interpersonal factors when addressing the issue of quality of life and sexual well-being. [A]

- Do not believe that sex is not important for elderly women and try always to 'break the ice' in clinical practice with very simple open questions to facilitate the dialogue on sexual health. [B]
- Diagnose and routinely treat signs and symptoms of GSM/VVA to avoid the vicious circle between sexual pain and other FSD. [B]
- Always take into account the biopsychosocial model when sexual symptoms at menopause are clinically relevant in order to establish the best treatment plan. [C]

Androgen therapy for perimenopausal and postmenopausal women

Causes of female androgen insufficiency

In women, levels of testosterone and the pre-androgens, androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) peak in the third to fourth decade of life and then decline with age, with the greatest decline observed in the years approaching menopause[1,2]. <2++> Pathological causes of low testosterone in women include primary ovarian insufficiency, bilateral oophorectomy at any age, hypopituitarism, adrenal insufficiency and iatrogenic ovarian suppression.

Research into the role of testosterone in women has been hampered by imprecision of measurement of testosterone at the low physiological levels found in women. The use of liquid chromatography and tandem mass spectrometry has enabled the measurement of testosterone at low levels, but the issue of inter-assay variability persists even with this methodology[3]. Other factors limiting the interpretation of testosterone levels in women include the synthesis of testosterone in peripheral target tissues so that serum levels may not accurately reflect tissue androgen exposure and that individual variations in androgen receptor sensitivity will modulate the effects of testosterone exposure.

Testosterone and female sexual function

Two recent, large, independent studies have shown strong correlations between levels of total and free testosterone, androstenedione and DHEAS and sexual desire in women aged 19–65 years[4], and between testosterone and masturbation frequency, sexual desire and arousal in women aged 42–52 years at recruitment to a 10-year follow-up study[5]. These studies provide the most robust data for the relationships between androgens and female sexual function. <2+>

Testosterone therapy for the treatment of female sexual dysfunction

The primary indication for testosterone is for the treatment of diminished sexual desire that causes the affected woman to experience significant distress (previously defined as hypoactive sexual desire disorder or HSDD[6]). Before testosterone therapy is considered, other causes of impaired sexual desire and/or arousal must be addressed. These include dyspareunia, depression, medication side-effects, relationship issues and other health problems affecting the woman or her partner.

Large, placebo-controlled RCTs have consistently show benefits of continuous testosterone therapy for women diagnosed with HSDD, with statistically significant improvements in sexual satisfaction, desire, arousal, pleasure and orgasm. <1++> These effects have been seen for naturally and surgically menopausal women, with and without concurrent MHT, and premenopausal women in their late reproductive years[7–9]. Testosterone is also effective for the management of antidepressant-associated desire-arousal disorder[10]. Most recently, HSDD and sexual arousal disorder have been re-classified as single entity: sexual interest-arousal disorder[11]. As arousal and desire are intrinsically linked, and as testosterone therapy improves both desire and arousal, women classified in this way should be managed as women previously diagnosed as having HSDD.

Androgenic side-effects of testosterone therapy are dose-related and avoidable with the use of formulations and doses appropriate for women. There is no evidence from large, placebo-controlled RCTs that transdermal testosterone in appropriate doses results in adverse cardiovascular or metabolic effects or effects on the endometrium[12,13]. Available data do not indicate an increase in risk of breast cancer with transdermal testosterone; no large study with this outcome has yet been published[7,12].

Intravaginal testosterone for treatment of vulvovaginal atrophy

Preliminary studies indicate intravaginal testosterone could provide an alternative for the treatment of VVA. <1–> Androgen receptors, aromatase (which converts testosterone to estradiol) and 5α-reductase isotypes 1 and 2 (convert testosterone to dihydrotestosterone, DHT) are present throughout the urogenital tract[14]. Intravaginal testosterone administered alone or with vaginal estrogen has been shown to improve dyspareunia, sexual desire, lubrication and satisfaction compared with placebo[15,16]. Beneficial effects have been seen with administration three times/week[16]. These studies are

promising; larger studies are required before intravaginal testosterone can be recommended in clinical practice.

Testosterone for the treatment of other aspects of women's health

Testosterone therapy has been shown to have favorable effects on bone health, with observational studies suggesting that higher testosterone levels are associated with reduced fracture risk. Fracture data from RCTs are lacking. Testosterone is not indicated for the prevention or treatment of osteoporosis. <2++>

Most observational studies show that low blood levels of total, free or bioavailable testosterone (free and albumin-bound testosterone) and low levels of sex hormone binding globulin (SHBG) are associated with a greater likelihood of atherosclerotic carotid disease, cardiovascular events and total mortality[17–19]. Testosterone has been shown to be a vasodilator in postmenopausal women[20,21] and one small RCT of testosterone therapy in women with congestive cardiac failure demonstrated favorable cardiovascular effects[22]. Testosterone therapy should not be used to prevent or treat cardiovascular disease in women. <2+>

RCTs indicate a favorable, but small effect of transdermal testosterone on cognitive performance in postmenopausal women[7,23,24]. Although these data justify further research in this field, they do not support the use of testosterone for the prevention of cognitive decline. <1−>

The systemic use of DHEA therapy for women

RCTs have not shown benefits of systemic DHEA therapy over that of placebo in terms of improved sexual function, well-being or metabolic health in postmenopausal women[12,25]. Oral DHEA has been shown to have marginal beneficial effects on health-related quality of life and depression in women with adrenal insufficiency, but not on sexual function[26]. <1+>

Intravaginal DHEA for treatment of vulvovaginal atrophy

Daily intravaginal application of DHEA has shown favorable effects for dyspareunia and symptomatic VVA[27], but these effects are not sustained when DHEA is administered twice a week[28]. <1−>

Key messages

- Androgen levels decline with age in women with no significant change associated with natural menopause. [A]
- There is strong evidence that androgens influence female sexual function and that testosterone therapy may be useful for women who have experienced loss of sexual desire and/or arousal. [A]
- Before testosterone therapy can be considered, women should be fully assessed for other treatable causes of their sexual dysfunction, and these should be addressed. [A]
- Testosterone therapy should be considered as a clinical trial, which should not be continued if a woman has not experienced a significant benefit by 6 months. [A]

Complementary therapies, non-pharmacological and lifestyle interventions

High-quality data from studies of non-pharmacological and lifestyle interventions for vasomotor symptoms have been limited.

The role of complementary therapies in the management of the menopause, both for symptomatic relief and avoidance of long-term complications, remains controversial. Studies and meta-analyses have not consistently supported the efficacy of complementary or over-the-counter therapies in reducing severity or frequency of hot flushes or night sweats[1]. <1+> Isoflavone preparations derived from soy and red clover and traditional Chinese medicines have been shown variable efficacy compared to placebo in small randomized trials and small meta-analyses[1–3]. <1−> Therapies such as Black cohosh and St John's Wort have been associated with adverse effects and interactions with medications and should therefore be used with caution and appropriate medical advice[4,5]. <1+> Further data from larger randomized trials are required to confirm the efficacy and safety of complementary therapies.

Meditation, relaxation, controlled breathing, cognitive behavioral therapy and mindfulness training show promise in managing hot flushes, but adequately powered randomized trials are still needed[6,7]. <1+> Randomized trials of acupuncture have not consistently shown a beneficial effect in reducing vasomotor symptoms, although recent meta-analyses suggest a small benefit[8–10]. <1−> Hypnosis has been shown to reduce the frequency of vasomotor symptoms and improve sleep quality[11]. <1−> Although exercise has beneficial effects on mood, cardiovascular and bone health, the evidence would suggest it has little role in managing vasomotor instability[12]. In fact for some women it may aggravate symptom severity. <1+> Stellate ganglion blockade has been shown to reduce vasomotor symptoms by 50% over a period of several months. It appears to be a safe and well-tolerated technique[13]. <1+>

Key messages

- Women should be counselled that complementary therapies have limited evidence for efficacy and safety and are not regulated by the medicines agencies. [B]
- Paced respiration, cognitive behavioral therapy, mindfulness training, acupuncture, hypnosis and stellate ganglion blockade may be useful techniques to consider when treating vasomotor symptoms. [A]

Bioidentical hormone therapy

The term 'bioidentical' means having the same molecular structure as a substance produced in the body[1]. Hence, estradiol and progesterone, as used in products manufactured by pharma companies and subjected to rigorous scrutiny by regulatory authorities, are bioidentical forms of MHT.

Bioidentical hormone therapy (BHT) is a poorly defined term commonly used as a marketing tool to describe compounded hormone preparations which contain mixtures of various hormones, including estradiol, estrone, estriol, progesterone, testosterone and DHEA, usually prepared by compounding pharmacies, but which *are not* subjected to the same rigorous manufacturing standards, quality control and regulatory oversight as pharmaceutical-grade registered products[1,2]. <2+> Bioidentical hormones are not 'natural'. They are synthesized in laboratories from plant-based precursors in the same way that regulated hormone products are prepared. <2+> Advertising and promotional claims made for the safety and efficacy of compounded BHT are not validated by medical evidence. <2+>

Proponents of BHT often claim, erroneously, that their preparations are made to meet individual needs of women, based on blood or salivary hormone levels. This concept is scientifically flawed, as the ratios of estrone and estriol to the parent estradiol in the body remain relatively constant, depending on the enzyme activity within cells, and it is futile for doctors to write prescriptions for all three hormones in an attempt to do what the body does naturally[1].

Endometrial cancer has been associated with estrogen-containing BHT. The progesterone used in these preparations may be insufficient to inhibit estrogen-induced endometrial stimulation. <3>

Hormonal assays of saliva are sometimes claimed to be a means of assessing hormonal needs and determining individual doses. There are no data to reliably support these claims. <2+>

Bioidentical compounded hormone therapy offers no proven advantages over similar regulated products and lacks the protection to the patient offered by strict regulation and oversight. The hormones available in these preparations are all available in safe regulated products. All mainstream scientific, clinical and regulatory bodies in women's health advise against the use of these products[3–7]. A prescriber of these products is at risk of future medicolegal claims.

Key messages

- Prescribing of compounded BHT is not recommended due to the lack of quality control and regulatory oversight associated with these products, together with lack of evidence of safety and efficacy. [B]
- The use of serum or salivary hormone levels is not recommended to assist in the management of MHT as these levels are of little value in selecting initial medication doses or in monitoring efficacy. [B]
- Women requesting compounded BHT should be encouraged to consider regulated products containing hormones which are structurally identical to those produced in the body. These are available in a wide range of doses and delivery methods. [B]

Vasomotor symptoms: pharmacologic treatments

The mechanisms underlying vasomotor symptoms (VMS) are still not well understood. Treatment of VMS without hormones is possible and may be the sole option in women with contraindications to estrogen or progesterone therapy. A variety of pharmacological agents decrease the frequency and intensity of hot flushes; however, head-to-head comparisons with hormone therapy or between non-hormonal agents are limited. Each pharmacological strategy has specific side-effects.

Within the drugs that have established alleviating actions on VMS are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), some antiepileptic drugs, and other centrally acting drugs. While each of these categories of drugs is effective in clinical trials, there have been very few head-to-head studies of non-hormonal agents for the treatment of hot flushes[1–4]. <1++>

Efficacy of several SSRIs, SNRIs and gabapentin has been demonstrated in placebo-controlled trials[5–14]. <1++> All clinical studies on agents targeting VMS are characterized by a relevant placebo effect, which can *per se* reduce hot flushes by up to 50%[15]. <1++>

Information on the comparative effects of non-hormonal preparations versus estrogen therapy is limited to gabapentin and venlafaxine. High doses of gabapentin

(300 mg three times per day) have been shown to reduce hot flushes similar to 0.625 mg estrogen[16]. However, at this dose gabapentin is associated with significant side-effects. Venlafaxine (75 mg/day) has also been shown to decrease hot flushes similar to a low dose of oral estradiol (0.5 mg) in a randomized trial[17]. A head-to-head study found that venlafaxine (37.5 mg per day increasing to 75 mg controlled release) is equally effective but better tolerated than gabapentin (300 mg once per day increasing to 300 mg three times per day) in breast cancer patients. Both products reduced the frequency and severity of hot flushes (by 66%) but side-effects were greater with gabapentin[18]. <1++>

Gabapentin may be specifically useful in patients experiencing night-time flushes with nocturnal sweats and repeated awakenings, due to its sedating effect. Intake of a single dose of gabapentin at bedtime has been suggested in these patients and this treatment schedule may help decrease side-effects. <4>

Comparisons of trials of venlafaxine, desvenlafaxine, paroxetine, citalopram, and escitalopram suggest that these molecules have similar efficacy on hot flushes[10]. <1++>

Sertraline and fluoxetine are not associated with significant reductions in hot flushes in placebo-controlled studies, and are therefore not recommended for treatment of VMS[7,19–21]. <1++>

Clonidine, an α-2 adrenergic agonist, is slightly more effective than placebo is reducing hot flushes in a meta-analysis of ten trials[2]. <1++> Clonidine use is associated with significant side-effects (dry mouth, dizziness, constipation, hypotension and sedation) that limit its clinical use. Transdermal preparations may be superior to oral ones due to more stable blood levels and may help increase compliance. <4>

Women with a history of breast cancer represent an important category of patients where non-hormonal treatments are useful for the treatment of VMS. SSRIs/SNRIs decrease hot flushes up to 50% in these patients, and this is acceptable in most cases. Efficacy is similar in women taking tamoxifen[22]. <1+>

SSRIs inhibit the activity of CYP2D6, the enzyme that converts tamoxifen to its active metabolite, endoxifen. Paroxetine and fluoxetine are the strongest CYP2D6 inhibitors, while venlafaxine, desvenlafaxine, citalopram and escitalopram are less effective[23–26]. Whether interference with CYP2D6 by SSRIs or SNRIs has any impact on breast cancer recurrence or survival is controversial, but this should be considered when selecting a treatment for hot flushes in these patients. If a SSRI/SNRI is to be used, compounds that interfere less with tamoxifen metabolism, such as venlafaxine and citalopram, should be preferred. SSRIs do not interfere with the action of aromatase inhibitors and can be used safely in women receiving these drugs. <4>

Duration of treatment of VMS with non-hormonal agents should be reviewed periodically, as with hormonal interventions. Initiation of treatment usually requires step-wise increases of dose to minimize side-effects. Similarly, discontinuation should be obtained by dose tapering over at least 2 weeks to avoid withdrawal symptoms. <4>

Key messages

- Venlafaxine, desvenlafaxine, paroxetine, citalopram, and escitalopram are effective in reducing hot flushes in postmenopausal women. [A]
- Paroxetine should be avoided in women receiving tamoxifen. [A]
- Gabapentin is as effective but has more side-effects compared to SSRIs/SNRIs. [B]

Postmenopausal vulvovaginal atrophy

After menopause, histological and functional changes in the vagina and urogenital epithelium appear due to a decline in estrogen levels and more than half of all postmenopausal women will experience symptoms associated with tissue atrophy.

A new definition for vulvovaginal atrophy (VVA) has been proposed by NAMS/ISSWSH. It has been named genitourinary syndrome of menopause (GSM), in order to describe more accurately the constellation of urogenital symptoms and signs associated with menopause and to remove the negative stigma of atrophy[1].

Women are poorly aware that VVA is a chronic condition with a significant impact on sexual health and quality of life and that effective and safe treatments may be available[2,3].

All local estrogen preparations (creams, pessaries, tablets, vaginal ring) are effective in decreasing signs and symptoms of vaginal atrophy but they differ slightly in their adverse-event profiles[5–8]. <1++> Ospemifene, a SERM derived from toremifene, has also been shown to be effective in treating vulval and vaginal atrophy[9–13]. <1++> Vaginal moisturizers and lubricants as well as regular sexual activity may be helpful to such women. Vaginal moisturizers may have an equivalent efficacy to topical vaginal estrogen and should be offered to women wishing to avoid the use of hormonal therapy[14]. <1+>

Key messages

- Health-care providers should be proactive in order to help their patients to disclose the symptoms

related to VVA and to seek adequate treatment when vaginal discomfort is clinically relevant. [B]
- Treatment should be started early, before irrevocable atrophic changes have occurred, and needs to be continued to maintain the benefits. [B]
- The principles of treatment in women with established VVA are both restoration of urogenital physiology and alleviation of symptoms; when VVA is the sole symptom, local estrogen treatment should be the first choice. [B]
- The choice of modality for local estrogen administration should be guided by patient preference. [D]
- Local estrogen therapy minimizes the degree of systemic absorption and, although vaginal administration can increase plasma levels of estrogens during chronic administration, the observed levels are not above the normal range of ≤ 20 pg/ml for postmenopausal women. [B]
- Additional progestogen is not indicated when appropriate low-dose, local estrogen is used, although long-term data (more than 1 year) are lacking. [B]
- If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness, and sexual activity should be recommended on a regular basis. [C]
- There are few data on the use of vaginal estrogens in women with gynecological hormone-responsive cancers so they should be used with discretion. [D]
- Use of local estrogen in women on tamoxifen or aromatase inhibitors needs careful counselling and discussion with the patient and the oncology team. [D]
- Estriol and testosterone preparations may be an option for such patients but more studies are needed. [C]

Novel menopause therapies

Urogenital

Daily topical use of DHEA is promising in the treatment of VVA and sexual associated symptoms, due to a favorable safety profile in women with contraindications to MHT[1]. Efficacy appears to be lost with twice-weekly maintenance administration[2]. <1++>

Ospemifene, a SERM recently approved at the dose of 60 mg orally, is indicated for the systemic treatment of moderate to severe dyspareunia associated with VVA in women who are unable to tolerate or unwilling to take local or systemic estrogens[3]. <1++> A positive cascade effect on other domains of sexual function has been documented. Another SERM, lasofoxifene, is under investigation.

Table 4. World Health Organization Council for International Organizations of Medical Sciences (CIOMS) classification of the frequency of drug reactions.

Very common	$>1/10$ ($>10\%$)
Common (frequent)	$>1/100$ and $<1/10$ ($>1\%$ and $<10\%$)
Uncommon (infrequent)	$>1/1000$ and $<1/100$ ($>0.1\%$ and $<1\%$)
Rare	$>1/10\,000$ and $<1/1000$ ($>0.01\%$ and $<0.1\%$)
Very rare	$<1/10\,000$ ($<0.01\%$)

Systemic

A CEE 0.45 mg/bazedoxifene 20 mg combination product (tissue selective estrogen complex) has recently been approved for the management of VMS[4]. <1++> This is potentially a useful option in women who are intolerant to the effects of progestogens. The combination lead to reduced breast density but further data are required to confirm its impact on breast cancer incidence[5].

Influence of methodology and epidemiology on MHT perception

There is a hierarchy of scientific evidence that should be taken into account when drawing conclusions from any scientific investigation. In general (from the highest standard or level of evidence to the lowest), the standards of evidence are replicated findings from high-quality RCTs, RCTs of lesser quality, cohort studies, other observational studies such as repeated cross-sectional samples, case–control studies, case series and case reports, and, lastly, expert opinion. However, even RCTs and cohort studies must be interpreted with caution, particularly with reference to MHT (see Table 1).

Observational studies (e.g. Nurses' Health Study) are primarily used for hypothesis generation and cannot demonstrate causality. Inherent biases in many observational studies of MHT typically include: selection bias – healthier women prescribed MHT; recall bias – recall of prior hormone usage may be influenced by later outcomes; prevention bias – monitoring and treating more intensively in women prescribed MHT; compliance bias – patients with greater adherence (even to placebo) have better outcomes; survivor bias – MHT may be stopped due to illness; prevalence-incidence bias – early adverse effects of MHT may not be observed if the user dies before becoming part of cohort.

RCTs (e.g. the WHI) are primarily used for hypothesis testing, to prove or disprove cause and effect. They can be downgraded in their level of evidence due to factors such as: poor compliance, dropout rate exceeding that accounted for in the study design, loss of blinding, deviation from protocol, inappropriate generalization of a single treatment to an entire class of treatments, and inappropriate generalization of results to groups for which the trial was inadequately powered. The WHI was

designed to test the outcomes associated with use of MHT in women more than a decade past menopause. Its results have been generalized to women near menopause who were not adequately represented, and for whom some WHI findings suggested important contrasts with benefit at younger ages. Similarly, the WHI tested only one form of oral estrogen and one form of oral progestogen. Generalization of those results to other doses, other compounds and other routes of administration strays beyond the bounds of proper methodology, all the more so when evidence from other study designs, spanning from histological, to metabolic, to cohort, suggests meaningful differences by dose, compound and route of administration.

The World Health Organization Council for International Organizations of Medical Sciences (CIOMS) has classified the frequency of drug reactions, which would include the impact of MHT or estrogen therapy (see Table 4). However, these frequencies do *not* necessarily correspond to statistical significance. Rare findings in large RCTs and observational studies may be statistically significant because of the large sample size, but may be of minor clinical importance in their application to a particular patient in the clinical setting. Failure to provide a clinical context is often a problem in understanding and interpreting study outcomes.

Conclusions and action points

These IMS evidence-based recommendations are intended to encourage optimal care of all women in midlife and beyond. With a rapidly growing population of women in midlife and beyond, it is imperative that further research continues in midlife women to optimize quality of life and long-term well-being.

The key principles to achieve this goal are as follows:

- The benefits and risks of MHT vary greatly in individual circumstances.
- Research over the last decade has shown that risks can be minimized and benefits maximized with selection of the optimal regimen at the optimal time.
- The safety of MHT largely depends on age and time since menopause.
- Healthy women younger than 60 years should not be unduly concerned about the safety profile of MHT.
- New data and re-analyses of older studies by women's age show that, for most women, the potential benefits of MHT given for a clear indication are many and the risks are few when initiated within a few years of menopause.
- Studies strongly suggest that it is the progestogen component of MHT that is more significant in any increase in breast cancer risk rather than the estrogen.
- Modern progestogens, natural progesterone and SERMs optimize metabolic and breast effects.
- Recent randomized trials such as the Danish Osteoporosis Prevention Study (DOPS) and studies using surrogate endpoints for long-term morbidities such as the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE) are now confirming the window of opportunity in early menopause when cardiovascular harm is avoided and benefits can be achieved.
- Increasing data indicate benefits for primary prevention of osteoporotic fractures and coronary artery disease and a reduction in all-cause mortality for women who initiate MHT around the time of menopause.

Key action points

- Health Departments/Regulators: Encourage change of policy towards menopause and MHT.
- The Prescribers: Expand education and training for health-care professionals to optimize menopause management.
- Media: Engage positively highlighting favorable data and putting risks into perspective.
- Pharma Industry: Reverse negative commercial/R&D decisions and encourage the exploration and development of novel regimens.
- The menopausal woman: Improve access to information to allow informed choice and increase proactive confidence to maintain menopausal health.
- MHT: Clarification of differences in action/risk profiles to maximize benefits and minimize adverse effects.

The Writing Group for the Recommendations

A summary of Declarations of interest in the past 2 years is listed below. A more detailed list is available on the IMS website.

R. J. Baber
Obstetrics and Gynaecology, Sydney Medical School North, The University of Sydney, Sydney, Australia
Advisory Board and/or Consultant: *Pfizer*
Speaker's Bureau: *Abbott*

N. Panay
Imperial College London, UK, Co-Editor-in-Chief, *Climacteric*

Advisory Board and/or Consultant: *Abbott, Bayer, Besins, Novo Nordisk, Pfizer, Shionogi*
Speaker's Bureau: *Abbott, Bayer, Besins, Novo Nordisk*

A. Fenton
Christchurch Women's Hospital, Christchurch, New Zealand, Co-Editor-in-Chief, *Climacteric*
Advisory Board and/or Consultant: *Pfizer*
Speaker's Bureau: *Besins, Mylan*

L. Cardozo
Professor of Urogynaecology, King's College Hospital, London, UK
Advisory Board and/or Consultant: *Astellas, BMR, Golin Health*
Speaker's Bureau: *Allergan, Astellas*
Grant/research support: *Pfizer*

C. Castelo-Branco
Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Barcelona, Spain
Advisory Board and/or Consultant: *Pierre Fabre, Shionogi*
Speaker's Bureau: *Amgem, Isdin, Pfizer, Pierre Fabre, Shionogi*

S. R. Davis
Women's Health Research Program, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
Advisory Board and/or Consultant: *Abbott International, Pfizer, Acerus Pharmaceuticals*
Grant/research support: *Lawley Pharmaceuticals*

T. J. de Villiers
MediClinic Panorama and Department of Obstetrics and Gynecology, Stellenbosch University, Cape Town, South Africa
Advisory Board and/or Consultant: *Adcock Ingram Ltd, Merck, Pfizer*
Speaker's Bureau: *Adcock Ingram Ltd, Pfizer*

S. R. Goldstein
Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY, USA
Advisory Board and/or Consultant: *AbbVie, Amgen, Cook ObGyn, JDS Therapeutics, Pfizer, Radius Health Inc, Sermonix Pharmaceuticals, Shionogi Ltd*
Speaker's Bureau: *JDS Therapeutics, Pfizer and Shionogi*
Equipment loan as a consultant: *Philips Ultrasound*

A. Gompel
UF de Gynécologie, Université Paris Descartes, AP-HP, Hopitaux Paris Centre, Port Royal Cochin, INSERM U1007, Paris, France
No relevant financial relationships

V. W. Henderson
Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, CA, USA
Grant/research support: *NIH*
Travel reimbursement: *American Academy of Neurology, International Menopause Society to participate in meetings of society committees*

H. N. Hodis
Atherosclerosis Research Unit, Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, USA
Grant/research support: *NIH as Principal investigator*

R. D. Langer
Associate Dean for Clinical and Translational Research and Professor of Family Medicine-Las Vegas, University of Nevada School of Medicine, Las Vegas, NV, USA
Litigation consultant: *Roche Pharmaceuticals*

R. A. Lobo
Department of Obstetrics and Gynecology, Columbia University, New York, NY, USA
Speaker's Bureau: *Pfizer*
Grant/research support: *Therapeutics MD*

P. M. Maki
Departments of Psychiatry and Psychology, University of Illinois at Chicago, USA
Speaker's Bureau: *Abbott, Noven*

A. O. Mueck
Department of Women's Health, Germany and Capital Medical University, Beijing OB/GYN Hospital, WHO Centre, China
No relevant financial relationships

R. E. Nappi
Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS S. Matteo Foundation, University of Pavia, Pavia, Italy
Advisory Board and/or Consultant: *Bayer HealthCare, Gedeon Richter, Merck Sharpe & Dohme, Shionogi Ltd*
Speaker's Bureau: *Novo Nordisk, Pfizer, Shionogi Ltd, TEVA Women's Health Inc*
Grant/research support: *Bayer HealthCare*

A. Pines
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
No relevant financial relationships

G. Plu-Bureau
Department of Gynecology, Hopitaux Universitaires Paris Centre, Paris Descartes University, Paris, France
No relevant financial relationships

D. Robinson
Department of Urogynaecology, King's College Hospital, London, UK
Advisory Board and/or Consultant: *Astellas, Pfizer, Allergan, Ferring*
Speaker's Bureau: *Astellas, Pfizer, Allergan*
Grant/research support: *Astellas, Pfizer, Allergan*

T. Simoncini
Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
Advisory Board and/or Consultant: *Abbott, Actavis*
Speaker's Bureau: *Abbott, Actavis*

S. Z. Vujovic
Medical Faculty, University of Belgrade and Clinic of Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia
No relevant financial relationships

Source of funding The costs of writing this paper have been supported entirely from the funds of the International Menopause Society.

References

Methodology

1. Royal College of Obstetricians and Gynaecologists. Development of RCOG Green-top Guidelines (Clinical Governance Advice No. 1). http://www.rcog.org.uk/green-top-development

Mid-life body changes

1. Sternfeld B, Wang H, Quesenberry CP Jr, *et al*. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health Across the Nation. *Am J Epidemiol* 2004;160:912–22
2. Guthrie JR, Dennerstein L, Dudley EC. Weight gain and the menopause: a 5-year prospective study. *Climacteric* 1999;2:205–11
3. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. *Arch Intern Med* 1991;151:97–102
4. Jacoby E, Goldstein J, Lopez A, Nunez E, Lopez T. Social class, family, and life-style factors associated with overweight and obesity among adults in Peruvian cities. *Prevent Med* 2003;37:396–405
5. Hajian-Tilaki KO, Heidari B. Prevalence of obesity, central obesity and the associated factors in urban population aged 20-70 years, in the north of Iran: a population-based study and regression approach. *Obes Rev* 2007;8:3–10
6. Fonken LK, Workman JL, Walton JC, *et al*. Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci USA* 2010;107:18664–9
7. Pan A, Lucas M, Sun Q, *et al*. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med* 2010;170:1884–91
8. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. *Arch Intern Med* 2008;168:1568–75
9. Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. *Int J Obes (Lond)* 2010;34:1265–74
10. Abdulnour J, Doucet E, Brochu M, *et al*. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. *Menopause* 2012;19:760–7
11. Poehlman E, Toth MJ, Gardner A. Changes in energy balance and body composition at menopause: a controlled longitudinal study. *Ann Intern Med* 1995;123:673–8
12. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. *Int J Obes Relat Metab Disord* 2000;24:226–31
13. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Menopause-related changes in body fat distribution. *Ann NY Acad Sci* 2000;904:502–6
14. Wietlisbach V, Marques-Vidal P, Kuulasmaa K, Karvanen J, Paccaud F. The relation of body mass index and abdominal adiposity with dyslipidemia in 27 general populations of the WHO MONICA Project. *Nutr Metab Cardiovasc Dis* 2013;23:432–42
15. Rogers NH, Perfield JW 2nd, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. *Endocrinology* 2009;150:2161–8
16. Stubbins RE, Najjar K, Holcomb VB, Hong J, Nunez NP. Oestrogen alters adipocyte biology and protects female mice from adipocyte inflammation and insulin resistance. *Diabetes Obes Metab* 2012;14:58–66
17. Davis SR, Castelo-Branco C, Chedraui P, *et al*. Understanding weight gain at menopause. *Climacteric* 2012;15:419–29
18. Raeder MB, Ferno J, Vik-Mo AO, Steen VM. SREBP activation by antipsychotic- and antidepressant-drugs in cultured human liver cells: relevance for metabolic side-effects? *Mol Cell Biochem* 2006;289:167–73
19. Yuksel H, Odabasi AR, Demircan S, *et al*. Effects of oral continuous 17beta-estradiol plus norethisterone acetate replacement therapy on abdominal subcutaneous fat, serum leptin levels and body composition. *Gynecol Endocrinol* 2006;22:381–7
20. Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in post-menopausal women. *Menopause* 2000;7:395–401
21. Chen Z, Bassford T, Green SB, *et al*. Postmenopausal hormone therapy and body composition – a substudy of the estrogen plus progestin trial of the Women's Health Initiative. *Am J Clin Nutr* 2005;82:651–6
22. Sorensen MB, Rosenfalck AM, Hojgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. *Obes Res* 2001;9:622–6
23. O'Sullivan AJ, Crampton LJ, Freund J, Ho KK. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in post-menopausal women. *J Clin Invest* 1998;102:1035–40
24. dos Reis CM, de Melo NR, Meirelles ES, Vezozzo DP, Halpern A. Body composition, visceral fat distribution and fat oxidation in postmenopausal women using oral or transdermal oestrogen. *Maturitas* 2003;46:59–68

Diagnosis of menopause

1. Harlow SD, Gass M, Hall JE, *et al*. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Climacteric* 2012;15:105–14
2. Gelbaya TA, Nardo LG, Fitzgerald CT, Horne G, Brison DR, Lieberman BA. Ovarian response to gonadotropins after laparoscopic salpingectomy or the division of fallopian tubes for hydrosalpinges. *Fertil Steril* 2006;85:1464–8
3. Gold EB, Colvin A, Avis N, *et al*. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. *Am J Pub Health* 2006;96:1226–35
4. Avis NE, Crawford SL, Greendale G, *et al*. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531–9
5. Soules MR, Sherman S, Parrott E, *et al*. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric* 2001;4:267–72

6. Harlow SD, Crawford S, Dennerstein L, Burger HG, Mitchell ES, Sowers MF. Recommendations from a multi-study evaluation of proposed criteria for staging reproductive aging. *Climacteric* 2007;10:112–19
7. Harlow SD, Cain K, Crawford S, *et al*. Evaluation of four proposed bleeding criteria for the onset of late menopausal transition. *J Clin Endocrinol Metab* 2006;91:3432–8
8. Harlow SD, Mitchell ES, Crawford S, *et al*. The ReSTAGE Collaboration: defining optimal bleeding criteria for onset of early menopausal transition. *Fertil Steril* 2008;89:129–40
9. Randolph JF, Jr, Zheng H, Sowers MR, *et al*. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J Clin Endocrinol Metab* 2011;96:746–54
10. Freeman EW, Gracia CR, Sammel MD, Lin H, Lim LC, Strauss JF, 3rd. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. *Fertil Steril* 2007;87:101–6
11. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. *Menopause* 2005;12:559–66
12. Huddleston HG, Cedars MI, Sohn SH, Giudice LC, Fujimoto VY. Racial and ethnic disparities in reproductive endocrinology and infertility. *Am J Obstet Gynecol* 2010;202:413–19
13. Randolph JF, Jr, Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. *J Clin Endocrinol Metab* 2004;89:1555–61
14. Randolph JF, Jr, Sowers M, Gold EB, *et al*. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. *J Clin Endocrinol Metab* 2003;88:1516–22

Premature ovarian insufficiency

1. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986;67:604–6
2. Ostberg JE, Storry C, Donald AE, *et al*. A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. *Clin Endocrinol* 2007;66:557–64
3. de Kleijn MJ, van der Schouw YT, Verbeek AL, *et al*. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;155:339–45
4. Rocca WA, Grossardt BR, Miller VM, *et al*. Premature menopause or early menopause and risk of ischemic stroke. *Menopause* 2012;19:272–7
5. Gallagher JC. Effect of early menopause on bone mineral density and fractures. *Menopause* 2007;14:567–71
6. Rocca WA, Bower JH, Maraganore DM, *et al*. Increased risk of cognitive impairment or dementia in women with underwent oophorectomy before menopause. *Neurology* 2007;69:1074–83
7. de Almeida DM, Benetti-Pinto CL, Makuch MY. Sexual function of women with premature ovarian failure. *Menopause* 2011;18:262–6
8. Vujovic S, Brincat M, Erel T, *et al*. EMAS position statement: Managing women with premature ovarian failure. *Maturitas* 2010;67:91–3
9. Qin Y, Jiao X, Simpson JL, Chen ZJ. Genetics of primary ovarian insufficiency: new developments and opportunities. *Hum Reprod Update* 2015;21:787–808
10. Pu D, Xing Y, Gao Y, Gu L, Wu J. Gene variation and premature ovarian failure: a meta analysis. *Eur J Obstet Gynecol Reprod Biol* 2014;182:226–37
11. Li J, Vujovic S, Dalgleish R, *et al*. Lack of associations between ESR1 gene polymorphism and premature ovarian failure in Serbian women. *Climacteric* 2014;17:247–51
12. Qin Y, Vujovic S, Li G, *et al*. Ethnic specificity of variants on the ESR1, HK3, BRSK1 genes and the 8q22.3 locus: no association with premature ovarian failure (POF) in Serbian women. *Maturitas* 2014;77:64–7
13. La Barbera AR, Miller MM, Ober C, Rebar RW. Autoimmune etiology in premature ovarian failure. *Am J Reprod Immunol Microbiol* 1988;16:115–22
14. Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009;360:606–14
15. Mishell DR Jr, Nakamura RM, Crosignani PG, *et al*. Serum gonadotropin and steroid patterns during the normal menstrual cycle. *Am J Obstet Gynecol* 1971;111:60–5
16. Hubayter ZR, Popat V, Vanderhoof VH, *et al*. A prospective evaluation of antral follicle function in women with 46,XX spontaneous primary ovarian insufficiency. *Fertil Steril* 2010;94:1769–74
17. Tartagni M, Cicinelli E, De Pergola G, *et al*. Effects of pretreatment with estrogens on ovarian stimulation with gonadotropins in women with premature ovarian failure: a randomized, placebo controlled trial. *Fertil Steril* 2007;87:858–61
18. Lee SJ, Schover LR, Partridge AH, *et al*. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917–31
19. Gubbala K, Laios A, Gallos I, *et al*. Outcomes of ovarian transposition in gynecological cancers; a systematic review and meta-analysis. *J Ovarian Res* 2014;7:69

Lifestyle, diet and exercise

1. Grindler NM, Santoro NF. Menopause and exercise. *Menopause* 2015 Sep 21. Epub ahead of print
2. Dubnov-Raz G, Pines A, Berry EM. Diet and lifestyle in managing postmenopausal obesity. *Climacteric* 2007;10(Suppl 2):38–41

Urogynecology

1. Robinson D, Toozs-Hobson P, Cardozo L. The effect of hormones on the lower urinary tract. *Menopause Int* 2013;19:155–62
2. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Synder T. Postmenopausal hormones and incontinence: the Heart and Estrogen/progestin Replacement Study. *Obstet Gynecol* 2001;97:116–20
3. Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol* 2004;103:254–60
4. Hendrix SL, Cochrane BR, Nygaard IE, *et al*. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005;293:935–48
5. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CMA. Oestrogen therapy for urinary incontinence in post-

menopausal women. *Cochrane Database Syst Rev* 2009, Issue 4. Art. No: CD001405
6. Moore K, Dumoulin C, Bradley C, *et al*. Adult conservative management. In Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. Paris: Health Publications Ltd, 2013:1101–228
7. Cardozo L, Lose G, McClish D, Versi E. A systematic review of the effects of oestrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynaecol Scand* 2004;83:892–7
8. Robinson D, Cardozo L, Milsom I, *et al*. Oestrogens and overactive bladder. *Neurourol Urodyn* 2014;33:1086–91
9. Andersson KE, Chapple CR, Cardozo L, *et al*. Pharmacological treatment of urinary incontinence. In Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. Paris: Health Publications Ltd, 2013:623–728
10. Dmochowski R, Athanasiou S, Reid F, *et al*. Surgery for urinary incontinence in women. In Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence*. Paris: Health Publications Ltd, 2013:1307–76
11. Sultana CJ, Walters MD. Oestrogen and urinary incontinence in women. *Maturitas* 1995;20:129–38
12. Brandberg A, Mellstrom D, Samsioe G. Low dose oral oestriol treatment in elderly women with urogenital infections. *Acta Obstet Gynaecol Scand* 1987;140:33–8
13. Cardozo L, Lose G, McClish D, *et al*. A systematic review of estrogens for recurrent urinary tract infections: Third report of the Hormones and Urogenital Therapy Committee. *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:15–20
14. Rees M, Pérez-López FR, Ceasu I, *et al*. EMAS. EMAS clinical guide: low-dose vaginal estrogens for postmenopausal vaginal atrophy. *Maturitas* 2012;73:171–4
15. Perrota C, Aznar M, Mejia R, Albert X, Nq CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev* 2008;16(2):CD005131
16. Rahn DD, Ward RM, Sanses TV, *et al*. Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines. *Int Urogynecol J* 2015;26:3–13
17. Cardozo LD, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: Second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92:722–7
18. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2003;(4):CD001500

Postmenopausal osteoporosis

1. de Villiers TJ. Bone health and osteoporosis in postmenopausal women. *Best Pract Res Clin Obstet Gynaecol* 2009;23:73–85
2. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999;353:878–82
3. ISCD Combined Official Position. 2013. www.ISCD.org
4. Trémollieres FA, Pouillès JM, Drewniak N, *et al*. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX model. *J Bone Min Res* 2010;25:1002–9
5. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women' s Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
6. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
7. de Villiers TJ, Gass MLS, Haines CJ, *et al*. Global Consensus Statement on Menopausal Hormone Therapy. *Climacteric* 2013;16:203–4
8. de Villiers TJ, Stevenson JC. The WHI: the effect of hormone replacement therapy on fracture prevention. *Climacteric* 2012;15:263–6
9. Bagger YZ, Tanko LB, Alexandersen P, *et al*. Two to three years of hormone replacement therapy in healthy women have long-term prevention effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004;34:728–31
10. Ettinger B, Ensrud KE, Wallace R, *et al*. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol* 2004;104:443–51
11. Cummings SR, Ettinger B, Delmas PD, et al. for the LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359:697–708
12. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril* 2009;92:1045–52
13. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds.; Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Reference Intakes for Vitamin D and Calcium*. Washington, DC: National Academies Press (US), 2011
14. Bolland MJ, Avenell A, Baron JA, *et al*. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691
15. Dawson-Hughes B, Mithal A, Bonjour JP, *et al*. IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 2010;21:1151–4
16. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, *et al*. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *Br Med J* 2009;339:b3692
17. Black DM, Delmas PD, Eastell R, *et al*. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22
18. Black DM, Cummings SR, Karpf DB, *et al*. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535–41
19. Shane E, Burr D, Abrahamsen B, *et al*. Atypical subtrochanteric and diaphyseal femoral fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014;29:1–23

20. Khosla S, Burr D, Caulley J, *et al*. Bisphosphonate-associated osteonecrosis of the jaw: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22:1479–91
21. Ettinger B, Black DM, Mitlak BH, *et al*. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282:637–45
22. Silverman SL, Christiansen C, Genant HK, *et al*. Efficacy of bazedoxifene in reducing new vertebral fracture rate in postmenopausal women with osteoporosis: results of a 3-year randomized, placebo- and active-controlled clinical trial. *J Bone Miner Res* 2008;12:1923–34
23. Neer RM, Arnaud CD, Zanchetta JR, *et al*. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434–41
24. Meunier PJ, Roux C, Seeman E, *et al*. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459–68
25. Recommendation to restrict the use of Protelos/Osseor (strontium ranelate). European Medicines Agency. EMA/258269/2013
26. Cummings SR, Martin JS, McClung MR, *et al*. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65

Skin, cartilage, connective tissues

1. Welton AJ, Vickers MR, Kim J, *et al*. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337;550–3
2. Karsdal MA, Bay-Jensen AC, Henriksen K, Christiansen C. The pathogenesis of osteoarthritis involves bone, cartilage and synovial inflammation: may estrogen be a magic bullet? *Menopause Int* 2012;18:139–46
3. Christgau S, Tanko LB, Cloos PA, *et al*. Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM). *Menopause* 2004;11:508–18
4. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum* 2006;54:3194–204
5. Masuda Y, Hirao T, Mizunuma H. Improvement of skin surface texture by topical estradiol treatment in climacteric women. *J Dermatol Treat* 2013;24:312–17
6. Verdier-Sévrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. *Climacteric* 2007;10:289–97
7. Surazynski A, Jarzabek K, Haczynski J, Laudanski P, Palka J, Wolczynski S. Differential effects of estradiol and raloxifene on collagen biosynthesis in cultured human skin fibroblasts. *Int J Mol Med* 2003;12:803–9

Cardiovascular disease

1. Maruthur NM, Wang N-Y, Appel LJ. Lifestyle interventions reduce coronary artery disease risk. Results from the PREMIER trial. *Circulation* 2009;119:2026–31
2. Lobo RA, Davis SR, de Villiers TJ, *et al*. Prevention of diseases after menopause. *Climacteric* 2014;17:540–56
3. Hodis HN, Collins P, Mack WJ, *et al*. The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective. *Climacteric* 2012;15:217–28
4. Hulley S, Grady D, Bush T, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13
5. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
6. Salpeter SR, Walsh JM, Greyber E, *et al*. Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med* 2006;21:363–6
7. Salpeter SR, Cheng J, Thabane L, *et al*. Bayesian meta-analysis of hormone therapy and mortality in younger women. *Ann Intern Med* 2009;122:1016–22
8. Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77
9. Salpeter SR, Walsh JME, Greyber E, *et al*. Mortality associated with hormone replacement therapy in younger and older women: A meta-analysis. *J Gen Intern Med* 2004;19:791–804
10. Salpeter SR, Buckley NS, Liu H, *et al*. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. *Am J Med* 2009;122:42–52
11. Boardman HM, Hartley L, Eisinga A, *et al*. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015;3:CD002229
12. Mikkola TS, Tuomikoski P, Lyytinen H, *et al*. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause* 2015;22:976–83
13. Schierbeck LL, Rejnmark L, Tofteng CL, *et al*. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. *BMJ* 2012;345:e6409
14. Harman SM, Black DM, Naftolin F, *et al*. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014;161:249–60
15. Hodis HN. ELITE – Does the trial outcome confirm or refute the timing hypothesis of hormone therapy? Presented at the *14th World Congress on Menopause*, May 1–4, 2014, Cancun, Mexico
16. Berlind IA, Andersen M, Citarella A, *et al*. Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins. *Menopause* 2015;22:369–76

Stroke

1. Henderson VW, Lobo RA. Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials. *Climacteric* 2012;15:229–34
2. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the

Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
3. Boardman HM, Hartley L, Eisinga A, *et al*. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015;3:CD002229
4. Renoux C, Dell'aniello S, Garbe E, *et al*. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519
5. Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* 2011;18:237–40

Coagulation, venous thromboembolism disease and MHT

1. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(23 Suppl 1):I4–8
2. Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. *Climacteric* 2012;15:235–40
3. Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women. *Front Horm Res* 2014;43:21–32
4. Roach RE, Lijfering WM, van Hylckama Vlieg A, *et al*. The risk of venous thrombosis in individuals with a history of superficial vein thrombosis and acquired venous thrombotic risk factors. *Blood* 2013;122:4264–9
5. Cushman M, Kuller LH, Prentice R, *et al*. Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573–80
6. Curb JD, Prentice RL, Bray PF, *et al*. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772–80
7. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
8. Smith NL, Blondon M, Wiggins KL, *et al*. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern Med* 2014;174:25–31
9. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227–31
10. Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428–32
11. Canonico M, Oger E, Plu-Bureau G, *et al*. Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840–5
12. Canonico M, Fournier A, Carcaillon L, *et al*. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340–5
13. Straczek C, Oger E, Yon de Jonage-Canonico MB, *et al*. Estrogen and Thromboembolism Risk (ESTHER) Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation* 2005;112:3495–500
14. Canonico M, Oger E, Conard J, *et al*. EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;4:1259–65
15. Olie V, Plu-Bureau G, Conard J, *et al*. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause* 2011;18:488–93
16. Blondon M, Van Hylckama Vlieg A, Wiggins KL, *et al*. Differential associations of oral estradiol and conjugated equine estrogen with hemostatic biomarkers. *J Thromb Haemost* 2014;12:879–86
17. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, *et al*. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071–8
18. Vehkavaara S, Silveira A, Hakala-Ala-Pietila T, *et al*. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost* 2001;85:619–25
19. Oger E, Alhenc-Gelas M, Lacut K, *et al*. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol* 2003;23:1671–6
20. Post MS, Christella M, Thomassen LG, *et al*. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: a randomized, placebo controlled study in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1116–21

Central nervous system

1. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. *J Steroid Biochem Mol Biol* 2014;142:90–8
2. Henderson VW. Gonadal hormones and cognitive aging: a midlife perspective. *Womens Health* 2011;7:81–93
3. Gleason CE, Dowling NM, Wharton W, *et al*. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study. *PLoS Med* 2015;12:e1001833
4. Espeland MA, Shumaker SA, Leng I, *et al*. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med* 2013;173:1429–36
5. Henderson VW, Sherwin BB. Surgical versus natural menopause: cognitive issues. *Menopause* 2007;14:572–9
6. Resnick SM, Maki PM, Rapp SR, *et al*. Effects of combination estrogen plus progestin hormone treatment on

cognition and affect. *J Clin Endocrinol Metab* 2006;91:1802–10
7. Resnick SM, Espeland MA, An Y, *et al*. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab* 2009;94:4152–61
8. Yaffe K, Vittinghoff E, Ensrud KE, *et al*. Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. *Arch Neurol* 2006;63:945–50
9. Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am J Med* 2005;118:1232–9
10. Mulnard RA, Cotman CW, Kawas C, *et al*. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000;283:1007–15
11. Henderson VW. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol* 2014;142:99–106
12. Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience* 2000;101:485–512
13. LeBlanc ES, Janowsky J, Chan BKS, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001;285:1489–99
14. Shumaker SA, Legault C, Kuller L, *et al*. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947–58
15. Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. *Neuroscience* 2006;138:1031–9
16. Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005;76:103–5
17. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol* 2011;69:163–9
18. Shao H, Breitner JCS, Whitmer RA, *et al*. Hormone therapy and AD dementia: new findings from the Cache County study. *Neurology* 2012;79:1846–52
19. Yaffe K, Krueger K, Sarkar S, *et al*. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med* 2001;344:1207–13
20. Yaffe K, Krueger K, Cummings SR, *et al*. Effect of raloxifene on the prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Am J Psychiatry* 2005;162:683–90
21. Henderson VW, Ala T, Sainani KL, *et al*. Raloxifene for women with Alzheimer disease: A randomized controlled pilot trial. *Neurology* 2015;85:1937–44
22. Kreijkamp-Kaspers S, Kok L, *et al*. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004;292:65–74
23. Henderson VW, St John JA, Hodis HN, *et al*. Long-term soy isoflavone supplementation and cognition in women: A randomized, controlled trial. *Neurology* 2012;78:1841–8
24. Büchtemann D, Luppa M, Bramesfeld A, Riedel-Heller S. Incidence of late-life depression: a systematic review. *J Affect Disord* 2012;142:172–9
25. Maki PM, Gast MJ, Vieweg A, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. *Neurology* 2007;69:1322–30
26. Schmidt PJ, Nieman L, Danace au MA, *et al*. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000;183:414–20
27. Soares CD, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001;58:529–34
28. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006;295:1824–30
29. Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. *Headache* 2003;43:470–8
30. Christianson MS, Mensah VA, Shen W. Multiple sclerosis at menopause: Potential neuroprotective effects of estrogen. *Maturitas* 2015;80:133–9
31. Wang P, Li J, Qiu S, Wen H, Du J. Hormone replacement therapy and Parkinson's disease risk in women: a meta-analysis of 14 observational studies. *Neuropsychiatric Dis Treat* 2015;11:59–66
32. Parkinson Study Group POETRY Investigators. A randomized pilot trial of estrogen replacement therapy in post-menopausal women with Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:757–60
33. Harden CL, Herzog AG, Nikolov BG, *et al*. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. *Epilepsia* 2006;47:1447–51

Breast cancer

1. Chlebowski RT, Hendrix SL, Langer RD, *et al*. WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;289:3243–53
2. Anderson GL, Chlebowski RT, Rossouw JE, *et al*. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas* 2006;55:103–15
3. Colditz GA, Hankinson SE, Hunter DJ, *et al*. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589–93
4. Bakken K, Fournier A, Lund E, *et al*. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2011;128:144–56
5. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419–27

6. Fournier A, Berrino F, Clavell-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103–11
7. Chlebowski RT, Anderson GL, Gass M, *et al*. WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010;304:1684–92
8. Anderson GL, Chlebowski RT, Aragaki AK, *et al*. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012;13:476–86
9. Chen WY, Manson JE, Hankinson SE, *et al*. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006;166:1027–32
10. Lundström E, Christow A, Kersemaekers W, *et al*. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. *Am J Obstet Gynecol* 2002;186:717–22
11. Kenemans P, Bundred NJ, Foidart JM, *et al*. LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009;10:135–46
12. Cordina-Duverger E, Truong T, Anger A, *et al*. Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. *PLoS One* 2013;8:e78016
13. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol–progestogen therapy. *Obstet Gynecol* 2009;113:65–73

Endometrial safety and bleeding

1. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;81:799–816
2. American College of Obstetricians and Gynecologists. Diagnosis of abnormal uterine bleeding in reproductive-aged women. Practice Bulletin no. 128. *Obstet Gynecol* 2012;120:197–206
3. Guido RS, Kanbour-Shakir A, Rulin MC, Christopherson WA. Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer. *J Reprod Med* 1995;40:553–5
4. Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. The Menopause Study Group. *Am J Obstet Gynecol* 1994;170:1213–23
5. Weiderpass E, Adami HO, Baron JA, *et al*. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999;91:1131–7
6. Lethaby A, Suckling J, Barlow D, Farquhar CM, Jepson RG, Roberts H. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev* 2004;CD000402
7. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370–5
8. Anderson GL, Judd HL, Kaunitz AM, *et al*. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1739–48
9. Allen N, Tsilidis K, Key T, *et al*. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol* 2010;172:1394–403
10. Somboonporn W, Panna S, Temtanakitpaisan T, Kaewrudee S, Soontrapa S. Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women: systematic review and meta-analysis. *Menopause* 2011;18:1060–6
11. Pickar JH, Yeh IT, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. *Fertil Steril* 2009;92:1018–24
12. Stovall DW, Utian WH, Gass ML, *et al*. The effects of combined raloxifene and oral estrogen on vasomotor symptoms and endometrial safety. *Menopause* 2007;14:510–17
13. Bjarnason K, Cerin A, Lindgren R, Weber T. Adverse endometrial effects during long cycle hormone replacement therapy. Scandinavian Long Cycle Study Group. *Maturitas* 1999;32:161–70
14. Erkkola R, Kumento U, Lehmuskoski S, Mattila L, Mustonen M. No increased risk of endometrial hyperplasia with fixed long-cycle estrogen-progestogen therapy after five years. *J Br Menopause Soc* 2004;10:9–13
15. Allen NE, Tsilidis KK, Key TJ, *et al*. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol* 2010;172:1394–403
16. Archer DF, Hendrix S, Gallagher JC, *et al*. Endometrial effects of tibolone. *J Clin Endocrinol Metab* 2007;92:911–18
17. Clarke MJ. Tamoxifen for early breast cancer. *Cochrane Database Syst Rev* 2008;CD000486
18. Goldstein SR, Scheele WH, Rajagopalan SK, Wilkie JL, Walsh BW, Parsons AK. A 12-month comparative study of raloxifene, estrogen, and placebo on the postmenopausal endometrium. *Obstet Gynecol* 2000;95:95–103
19. Ronkin S, Northington R, Baracat E, *et al*. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. *Obstet Gynecol* 2005;105:1397–404
20. Constantine GD, Goldstein SR, Archer DF. Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. *Menopause* 2015;22:36–43
21. Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, Ylikorkala O; Ospemifene Study Group. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. *Climacteric* 2014;17:173–82
22. Goldstein SR, Neven P, Cummings S, *et al*. Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecologic outcomes. *Menopause* 2011;18:17–22

Ovarian cancer

1. de Villiers TJ, Pines A, Panay N, *et al*. International Menopause Society. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013;16:316–72
2. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet* 2015;385:1835–42
3. Gompel A, Burger H. A Commentary on a recent update of the ovarian cancer risk attributable to menopausal hormone therapy. *Climacteric* 2015;18:376–8

Lung cancer

1. Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108
2. Weir HK, Thompson TD, Soman A, Møller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020. *Cancer* 2015;121:1827–37
3. Gallagher LG, Rosenblatt KA, Ray RM, *et al*. Reproductive factors and risk of lung cancer in female textile workers in Shanghai, China. *Cancer Causes Control* 2013;24:1305–14
4. Pesatori AC, Carugno M, Consonni D, *et al*. Reproductive and hormonal factors and the risk of lung cancer: the EAGLE study. *Int J Cancer* 2013;132:2630–9
5. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of lung cancer – systematic review and meta-analysis. *Maturitas* 2010;65:198–204
6. Clague J, Reynolds P, Sullivan-Halley J, *et al*. Menopausal hormone therapy does not influence lung cancer risk: results from the California Teachers Study. *Cancer Epidemiol Biomarkers Prev* 2011;20:560–4
7. Chlebowski RT, Anderson GL, Manson JE, *et al*. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *J Natl Cancer Inst* 2010;102:1413–21
8. Chlebowski RT, Schwartz AG, Wakelee H, *et al*. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009;374:1243–51
9. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
10. Schwartz AG, Ray RM, Cote ML, *et al*. Hormone use, reproductive history and risk of lung cancer: the Women's Health Initiative studies. *J Thorac Oncol* 2015;10:1004–13

Colorectal cancer

1. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014;383:1490–502
2. Grodstein F, Martinez ME, Platz EA, *et al*. Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med* 1998;128:705–12
3. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106:574–82
4. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
5. Anderson GL, Limacher M, Assaf AR, *et al*. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
6. Prentice RL, Pettinger M, Beresford SA. Colorectal cancer in relation to postmenopausal estrogen and estrogen plus progestin in the Women's Health Initiative clinical trial and observational study. *Cancer Epidemiol Biomarkers Prev* 2009;18:1531–7
7. Manson JE, Chlebowski RT, Stefanick ML, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353–68
8. Morois S, Fournier A, Clavel-Chapelon F, *et al*. Menopausal hormone therapy and risks of colorectal adenomas and cancers in the French E3N prospective cohort: true associations or bias? *Eur J Epidemiol* 2012;27:439–52
9. Cummings SR, Ettinger B, Delmas PD, *et al*. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359:697–708

Cervical cancer

1. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/cervix/incidence/uk-cervical-cancer-incidence-statistics (section reviewed 11(06/2014)
2. Marsden J, Sturdee D. Cancer issues. *Best Pract Res Clin Obstet Gynaecol* 2009;23:87–107
3. Yasmeen S, Romano PS, Pettinger M, *et al*. Incidence of cervical cytological abnormalities with aging in the Women's Health Initiative: a randomized controlled trial. *Obstet Gynecol* 2006;108:410–19
4. Sawaya GF, Grady D, Kerlikowske K, *et al*. The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *Ann Intern Med* 2000;133:942–50
5. Jaakkola S, Pukkala E, Lyytinen HK, Ylikorkala O. Postmenopausal estradiol–progestagen therapy and risk for uterine cervical cancer. *Int J Cancer* 2012;131:E537–43

Upper gastrointestinal cancers

1. Fernandez E, Gallus S, Bosetti C, Franceschi S, Negri E, La Vecchia C. Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. *Int J Cancer* 2003;105:408–12
2. McGlynn KA, Sahasrabuddhe VV, Campbell PT, *et al*. Reproductive factors, exogenous hormone use and risk of hepatocellular carcinoma among US women: results from the Liver Cancer Pooling Project. *Br J Cancer* 2015;112(Suppl):1266–72

3. Freedman ND, Chow WH, Gao YT, *et al*. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut* 2007;56:1671–7
4. Lindblad M, García Rodríguez LA, Chandanos E, Lagergren J. Hormone replacement therapy and risks of oesophageal and gastric adenocarcinomas. *Br J Cancer* 2006;94:136–41
5. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2012;21:20–38
6. Wang BJ, Zhang B, Yan SS, *et al*. Hormonal and reproductive factors and risk of esophageal cancer in women: a meta-analysis. *Dis Esophagus* 2015 Mar 23. Epub ahead of print
7. Gallus S, Negri E, Chatenoud L, Bosetti C, Franceschi S, La Vecchia C. Post-menopausal hormonal therapy and gallbladder cancer risk. *Int J Cancer* 2002;99:762–3

General and sexual quality of life in the menopause

1. Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: Evidence from two US population based cross sectional surveys of ageing. *BMJ* 2010;340:c810
2. Ayers B, Hunter MS. Health-related quality of life of women with menopausal hot flushes and night sweats. *Climacteric* 2013;16:235–9
3. Appa AA, Creasman J, Brown JS, *et al*. The impact of multimorbidity on sexual function in middle-aged and older women: beyond the single disease perspective. *J Sex Med* 2014;11:2744–55
4. Avis NE, Brockwell S, Randolph JF Jr, *et al*. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. *Menopause* 2009;16:442–52
5. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001;76:456–60
6. Lonnèe-Hoffmann RA, Dennerstein L, Lehert P, Szoeke C. Sexual function in the late postmenopause: a decade of follow-up in a population-based cohort of Australian women. *J Sex Med* 2014;11:2029–38
7. Erekson EA, Martin DK, Ratner ES. Oophorectomy: the debate between ovarian conservation and elective oophorectomy. *Menopause* 2013;20:110–14
8. Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric* 2012;15:481–9
9. Panjari M, Bell RJ, Davis SR. Sexual function after breast cancer. *J Sex Med* 2011;8:294–302
10. Bitzer J, Giraldi A, Pfaus J. A standardized diagnostic interview for hypoactive sexual desire disorder in women: standard operating procedure (SOP Part 2). *J Sex Med* 2013;10:50–7
11. Wierman ME, Arlt W, Basson R, *et al*. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:3489–510
12. Levine K, Williams R, Harmann K. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause* 2008;15:661–6
13. Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. *Climacteric* 2014;17:3–9
14. Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Climacteric* 2014;17:557–63
15. Nappi RE, Davis SR. The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. *Climacteric* 2012;15:267–74
16. Nappi RE, Domoney C. Pharmacogenomics and sexuality: a vision. *Climacteric* 2013;16(Suppl 1):25–30
17. Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. *Expert Opin Pharmacother* 2015;16:875–87
18. Pines A, Sturdee DW, MacLennan AH. Quality of life and the role of menopausal hormone therapy. *Climacteric* 2012;15:213–16
19. Nastri CO, Lara LA, Ferriani RA, *et al*. Hormone therapy for sexual function in perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2013, Issue 6. Art. No.: CD009672
20. Biglia N, Maffei S, Lello S, Nappi RE. Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. *Gynecol Endocrinol* 2010;26:804–14

Androgen therapy for perimenopausal and postmenopausal women

1. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847–53
2. Haring R, Hannemann A, John U, *et al*. Age-specific reference ranges for serum testosterone and androstenedione concentrations in women measured by liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab* 2012;97:408–15
3. Legro RS, Schlaff WD, Diamond MP, *et al*. Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. *J Clin Endocrinol Metab* 2010;95:5305–13
4. Wahlin-Jacobsen S, Pedersen AT, Kristensen E, *et al*. Is there a correlation between androgens and sexual desire in women? *J Sex Med* 2015;12:358–73
5. Randolph JF, Jr, Zheng H, Avis NE, Greendale GA, Harlow SD. Masturbation frequency and sexual function domains are associated with serum reproductive hormone levels across the menopausal transition. *J Clin Endocrinol Metab* 2015;100:258–66
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington DC: American Psychiatric Press, 1994
7. Wierman ME, Arlt W, Basson R, *et al*. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:3489–510
8. Davis SR, Papalia MA, Norman RJ, *et al*. Safety and efficacy of a testosterone metered-dose transdermal spray for

treatment of decreased sexual satisfaction in premenopausal women: a placebo-controlled randomized, dose-ranging study. *Ann Intern Med* 2008;148:569–77
9. Goldstat R, Briganti E, Tran J, Wolfe R, Davis S. Transdermal testosterone improves mood, well being and sexual function in premenopausal women. *Menopause* 2003;10:390–8
10. Fooladi E, Bell RJ, Jane F, Robinson PJ, Kulkarni J, Davis SR. Testosterone improves antidepressant-emergent loss of libido in women: findings from a randomized, double-blind, placebo-controlled trial. *J Sex Med* 2014;11:831–9
11. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA, USA: American Psychiatric Publishing, 2013
12. Elraiyah T, Sonbol MB, Wang Z, *et al*. Clinical review: The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2014;99:3536–42
13. Davis SR, Moreau M, Kroll R, *et al*. Testosterone for low libido in menopausal women not taking estrogen therapy. *N Engl J Med* 2008;359:2005–17
14. Berman JR, Almeida FG, Jolin J, *et al*. Correlation of androgen receptors, aromatase, and 5-alpha reductase in the human vagina with menopausal status. *Fertil Steril* 2003;79:925–31
15. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *J Sex Med* 2010;7:1284–90
16. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. *J Sex Med* 2014;11:1262–70
17. Sievers C, Klotsche J, Pieper L, *et al*. Low testosterone levels predict all-cause mortality and cardiovascular events in women: a prospective cohort study in German primary care patients. *Eur J Endocrinol* 2010;163:699–708
18. Laughlin GA, Goodell V, Barrett-Connor E. Extremes of endogenous testosterone are associated with increased risk of incident coronary events in older women. *J Clin Endocrinol Metab* 2010;95:740–7
19. Ouyang P, Vaidya D, Dobs A, *et al*. Sex hormone levels and subclinical atherosclerosis in postmenopausal women: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 2009;204:255–61
20. Worboys S, Kotsopoulos D, Teede H, McGrath BP, Davis SR. Parental testosterone improves endothelium-dependent and independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab* 2001;86:158–61
21. Davison S, Thipphawong J, Blanchard J, *et al*. Pharmacokinetics and acute safety of inhaled testosterone in postmenopausal women. *J Clin Pharmacol* 2005;45:177–84
22. Lellamo F, Volterrani M, Caminiti G, *et al*. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. *J Am Coll Cardiol* 2010;56:1310–16
23. Davis SR, Davison SL, Gavrilescu M, *et al*. Effects of testosterone on visuospatial function and verbal fluency in postmenopausal women: results from a functional magnetic resonance imaging pilot study. *Menopause* 2014;21:410–14
24. Davison SL, Bell RJ, Gavrilescu M, *et al*. Testosterone improves verbal learning and memory in postmenopausal women: Results from a pilot study. *Maturitas* 2011;70:307–11
25. Davis SR, Panjari M, Stanczyk FZ. Dehydroepiandrosterone (DHEA) replacement for postmenopausal women. *J Clin Endocrinol Metab* 2011;96:1642–53
26. Alkatib AA, Cosma M, Elamin MB, *et al*. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009;94:3676–81
27. Labrie F, Archer D, Bouchard C, *et al*. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause* 2009;16:923–31
28. Bouchard C, Labrie F, Archer DF, *et al*. Decreased efficacy of twice-weekly intravaginal dehydroepiandrosterone on vulvovaginal atrophy. *Climacteric* 2015;18:590–607

Complementary therapies

1. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Menstrual Disorders and Subfertility Group. *Cochrane Database Syst Rev* 2013;12:CD001395
2. Shakeri F, Taavoni S, Goushegir A, Haghani H. Effectiveness of red clover in alleviating menopausal symptoms: a 12-week randomized, controlled trial. *Climacteric* 2015;18:568–73
3. Taylor-Swanson L, Thomas A, Ismail R, *et al*. Effects of traditional Chinese medicine on symptom clusters during the menopausal transition. *Climacteric* 2015;18:142–56
4. Lim TY, Considine A, Quaglia A, Shawcross DL. Subacute liver failure secondary to black cohosh leading to liver transplantation. *BMJ Case Rep* 2013;2013. pii: bcr2013009325
5. Liu Y-R, Jiang Y-L, Huang R-Q, Yang J-Y, Xiao B-K, Dong J-X. Hypericum perforatum L. preparations for menopause: a meta-analysis of efficacy and safety. *Climacteric* 2014;17:325–35
6. Carpenter JS, Burns DS, Wu J, *et al*. Paced respiration for vasomotor and other menopausal symptoms: a randomized, controlled trial. *J Gen Intern Med* 2013;28:193–200
7. Norton S, Chilcot J, Hunter MS. Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects. *Menopause* 2014;21:574–8
8. Castelo Branco de Luca A, Maggio da Fonseca A, Carvalho Lopes CM, Bagnoli VR, Soares Jr JM, Baracat EC. Acupuncture-ameliorated menopausal symptoms: single-blind, placebo-controlled, randomized trial. *Climacteric* 2011;14:140–5
9. Chiu HY, Shyu YK, Chang PC, Tsai PS. Effects of acupuncture on menopause-related symptoms in breast cancer survivors: a meta-analysis of randomized controlled trials. *Cancer Nurs* 2015 Jun 3. Epub ahead of print
10. Chiu HY, Pan CH, Shyu YK, Han BC, Tsai PS. Effects of acupuncture on menopause-related symptoms and quality of life in women in natural menopause: a meta-analysis

of randomized controlled trials. *Menopause* 2015;22: 234–44
11. Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. *Menopause* 2013;20:291–8
12. Daley AJ, Thomas A, Roalfe AK, *et al*. The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. *BJOG* 2015; 122:565–75
13. Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. *Menopause* 2014;21:807–14

Bioidentical hormone therapy

1. Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. *Menopause* 2004;11:356–67
2. MacLennan AH, Sturdee DW. The 'bioidentical/bioequivalent' hormone scam. *Climacteric* 2006;9:1–3
3. The Endocrine Society: Position Statement: Bioidentical Hormones, October 2006: http://www.endosociety.org
4. Huntley AL. Compounded or confused? Bioidentical hormones and menopausal health. *Menopause Int* 2011;17:16–18
5. Schmidt P. The 2012 Hormone Therapy Position Statement of the North American Menopause Society. *Menopause* 2012;19:257–71
6. Compounded bioidentical menopausal hormone therapy. Committee Opinion No. 532. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:411–15
7. de Villers TJ, Gass ML, Haines CJ, *et al*. Global Consensus Statement on Menopausal Hormone Therapy. *Climacteric* 2013;16:203–4

Vasomotor symptoms: MHT and pharmacologic treatments

1. Loprinzi CL, Sloan J, Stearns V, *et al*. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol* 2009;27:2831–7
2. Nelson HD, Vesco KK, Haney E, *et al*. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057–71
3. Rada G, Capurro D, Pantoja T, *et al*. Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database Syst Rev* 2010;(9):CD004923
4. Sideras K, Loprinzi CL. Nonhormonal management of hot flashes for women on risk reduction therapy. *J Natl Compr Canc Netw* 2010;8:1171–9
5. Loprinzi CL, Kugler JW, Sloan JA, *et al*. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059–63
6. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003;289:2827–34
7. Loprinzi CL, Sloan JA, Perez EA, *et al*. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578–83
8. Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. *Obstet Gynecol* 2005;105:161–6
9. Stearns V, Slack R, Greep N, *et al*. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005;23:6919–30
10. Loprinzi CL, Barton DL, Sloan JA, *et al*. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. *Menopause* 2008;15:655–60
11. Barton DL, LaVasseur BI, Sloan JA, *et al*. Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes: NCCTG trial N05C9. *J Clin Oncol* 2010;28:3278–83
12. Freeman EW, Guthrie KA, Caan B, *et al*. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 2011;305:267–74
13. Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337–45
14. Pandya KJ, Morrow GR, Roscoe JA, *et al*. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:818–24
15. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol* 2001;19:4280–90
16. Reddy SY, Warner H, Guttuso T Jr, *et al*. Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006;108:41–8
17. Joffe H, Guthrie KA, LaCroix AZ, *et al*. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. *JAMA Intern Med* 2014;174:1058–66
18. Bordeleau L, Pritchard KI, Loprinzi CL, *et al*. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol* 2010;28:5147–52
19. Suvanto-Luukkonen E, Koivunen R, Sundström H, *et al*. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12:18–26
20. Kerwin JP, Gordon PR, Senf JH. The variable response of women with menopausal hot flashes when treated with sertraline. *Menopause* 2007;14:841–5
21. Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. *Obstet Gynecol* 2007;109:823–30
22. Bardia A, Novotny P, Sloan J, Barton D, Loprinzi C. Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. *Menopause* 2009;16:477–83
23. Jin Y, Desta Z, Stearns V, *et al*. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;97:30–9
24. Kelly CM, Juurlink DN, Gomes T, *et al*. Selective serotonin reuptake inhibitors and breast cancer mortality in women

receiving tamoxifen: a population based cohort study. *BMJ* 2010;340:c693
25. Noehr-Jensen L, Zwisler ST, Larsen F, Sindrup SH, Damkier P, Brosen K. Escitalopram is a weak inhibitor of the CYP2D6-catalyzed O-demethylation of (+)-tramadol but does not reduce the hypoalgesic effect in experimental pain. *Clin Pharmacol Ther* 2009;86:626–33
26. Lash TL, Pedersen L, Cronin-Fenton D, *et al*. Tamoxifen's protection against breast cancer recurrence is not reduced by concurrent use of the SSRI citalopram. *J Cancer* 2008;99:616–21

Postmenopausal vulvovaginal atrophy

1. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Climacteric* 2014;17:557–63
2. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) – results from an international survey. *Climacteric* 2012;15:36–44
3. Nappi RE, Kingsberg S, Maamari R, Simon J. The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) Survey: Implications of vaginal discomfort in postmenopausal women and in male partners. *J Sex Med* 2013;10:2232–41
4. Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause* 2010;17:194–203
5. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. *Climacteric* 2015;18:121–34
6. Simon JA, Maamari RV. Ultra-low-dose vaginal estrogen tablets for the treatment of postmenopausal vaginal atrophy. *Climacteric* 2013;16(Suppl 1):37–43
7. Suckling J, Kennedy R, Lethaby A, Roberts H. Local estrogen therapy for vaginal atrophy in post menopausal women. *Cochrane Database Syst Rev* 2006 Issue 4 CD 001500
8. Sturdee DW, Panay N, on behalf of the IMS Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010;13:509–22
9. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. *Climacteric* 2015;18:226–32
10. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning. *J Sex Med* 2009;6:603–16
11. Nappi RE, Panay N, Bruyniks N, Castelo-Branco C, de Villiers TJ, Simon JA. The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. *Climacteric* 2015;18:233–40
12. Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. *J Steroid Biochem Mol Biol* 2014;142:142–54
13. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. *Maturitas* 2014;78:91–8
14. Sinha A, Ewies AA. Non-hormonal topical treatment of vulvovaginal atrophy: an up-to-date overview. *Climacteric* 2013;16:305–12

Novel menopause therapies

1. Archer DF, Labrie F, Bouchard C, *et al*. other participating members of the VVA Prasterone Group. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). *Menopause* 2015;22:950–63
2. Bouchard C, Labrie F, Archer DF, *et al*. VVA Prasterone Group. Decreased efficacy of twice-weekly intravaginal dehydroepiandrosterone on vulvovaginal atrophy. *Climacteric* 2015;18:590–607
3. Nappi RE, Panay N, Bruyniks N, Castelo-Branco C, de Villiers TJ, Simon JA. The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. *Climacteric* 2015;18:233–40
4. Pinkerton JV, Komm BS, Mirkin S. Tissue selective estrogen complex combinations with bazedoxifene/conjugated estrogens as a model. *Climacteric* 2013;16:618–28
5. Smith CL, Santen RJ, Komm B, Mirkin S. Breast-related effects of selective estrogen receptor modulators and tissue-selective estrogen complexes. *Breast Cancer Res* 2014;16:212