International Menopause Society (IMS) Recommendations and Key Messages on Women's Midlife Health and Menopause

Authors

Publication Steering Committee

Nick Panay[(a)], Anna Fenton[(b,c,d)], Haitham Hamoda[(e)], Timothy Hillard[(f)], Rakibul Islam[(g,h)], Hugo Pedder[(i)], Lorena Romero[(j)], Amanda J Vincent[(k)] (IMS Publication Steering Committee);

& the IMS Recommendations Writing Group:

Ang Seng Bin, Roopen Arya, Rod Baber, Niki Bezzant, Donal Brennan, Paula Briggs, Simon Brown, Antonio Cano, Peter Chedraui, Rachel Clapham, Premitha Damodaran, Susan R Davis, Gustavo Duque, Carolyn Ee, Sadaf Ghaem-Maghami, Steven Goldstein, Anne Gompel, Mathis Heydtmann, Howard Hodis, Nicole Jaff, Alicia Jones, Ekta Kapoor, Robert D. Langer, Jean-Jasmin Mi-Li Lee, Pauline Maki, Rossella E. Nappi, Matthew Nudy, James Pickar, Amos Pines, JoAnn Pinkerton, Walta Rocca, Elaine Robertson, Marla Shapiro C.M., Richard Simcock, Tommaso Simoncini, John Stevenson, Tobie de Villiers, Wendy Wolfman

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Ieman Al-Kanini, Rebecca Cheshire, Laura Cucinella, Gayathri Delanerolle, George Eleje, Belén Escudero Gonzalez, Nora Giese, Nur K. Abdul Jafar, Anna Kamola, Jing Liu, Evangeline Mantzioris, Millie Mardon, Alison Maunder, Joelle Metri, Tharanga Mudalige, Nailton José Neto, Vindya Pathiraja, Vibhuti Rao, Geovanna Souza, Caroline Thomas, Sophia Torkel, Jacob Van Doorn, Miriam Weber, Ece Kilic Weishaar, Shelby Wood, Katrina Wugalter and Emily (Guoyan) Yang.

[a] Queen Charlotte's and Chelsea Hospital, Imperial College London, London, UK;
[b] Department of Endocrinology, Christchurch Hospital, Christchurch, New Zealand;
[c] Oxford Women's Health, Christchurch, New Zealand;
[d] University of Otago School of Medicine, Department of Psychological Medicine;
[e] King's College Hospital, London, UK;
[f] Consultant Gynaecologist, University Hospitals Dorset, Poole, UK;
[g] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia;
[h] South Asian Institute for Social Transformation (SAIST), Dhaka, Bangladesh;
[i] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK;
[j] The Ian Potter Library, The Alfred, Melbourne, Australia;
[k] Monash Centre for Health Research and Implementation, Monash University, Clayton, Australia

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Key Words

Menopause, menopause hormone therapy, women's midlife health, premature ovarian insufficiency, vasomotor symptoms, genitourinary syndrome of menopause, vulvovaginal atrophy, androgen therapy, International Menopause Society, recommendations, guidelines

Abstract

Following a rigorous systematic review of the literature, the International Menopause Society (IMS) has produced detailed new recommendations and key messages on women's midlife health, menopause and menopause hormone therapy (MHT) to help guide healthcare professionals to optimize their support and guidance to women at this critical stage of life. The term MHT has been used to cover therapies including estrogens, progestogens, gonadomimetics and combined regimens. These IMS recommendations and key messages have been generated following a comprehensive systematic review process and contain the full text, references, figures and supplementary materials. The document has been made available online on the IMS website as live updatable guidance and is the reference source for the summary recently published in Climacteric (https://www.tandfonline.com/doi/full/10.1080/13697137.2025.2585487)

The quality of evidence and the strength of recommendations used in this guideline are based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) and the Appraisal of Guidelines for Research & Evaluation II (AGREE II) approaches. The new recommendations now include levels of evidence, grades of recommendations, good practice points and key messages.

The full text recommendations were developed by a body of 38 authors and 27 support team members derived from the IMS and other organisations. Global stakeholder surveys, targeted at both healthcare providers and consumers, were initially conducted to identify the key questions. A Publication Steering Committee (PSC) provided oversight of the process through regular meetings and ensured consistency of methodology.

By the end of the process, 30 completed sections were submitted by the authors to individual lead reviewers selected from the PSC to provide peer review and finally endorsed by the PSC, IMS board and stakeholders. Overall, 342 recommendations (285 supported by research data and 57 good practice points) and 40 key messages were formulated. These span a diverse range of health topics, including lifestyle, midlife body changes, vasomotor symptoms, genitourinary syndrome of menopause, osteoporosis, cardiometabolic health, dementia, premature ovarian insufficiency and various malignancies. A new section addresses the often-overlooked topic of sarcopenia which requires urgent attention. Current controversial topics, such as the influence of the media, the role of the pharmaceutical industry and publication ethics, are also explored.

The overall aim of these recommendations and guidelines is to provide the blueprint for support and guidance to women on midlife health and menopause, given the latest available evidence. In preparing these international recommendations, experts have endeavored to consider geographical variations in medical care, prevalence of diseases/conditions, symptom severity, availability and licensing of MHT and alternatives, and country-specific attitudes of the public, medical community and health authorities towards menopause management.

Introduction

We are now living in an era where information about women's midlife health and menopause is much more easily accessible by healthcare professionals (HCPs) and the public. However, the quality of this information is variable and can often be polarized, misleading and disempowering [1,2]. Messaging from social media towards the management of menopause has significantly influenced how women manage their individual menopause experience. With this background, it was imperative that the International Menopause Society (IMS) provided updated information which was derived from rigorous systematic reviews of the best research available to facilitate evidence-based management by HCPs. A recent publication that formally appraised menopause guidance emphasized the importance of only extracting and comparing the recommendations from the most robust national and international documents [3]. It is hoped that the robust methodology applied in producing this latest IMS guidance will optimize the provision of high-quality, locally relevant information, thus empowering women to personalize their menopause management choices.

The IMS is grateful to the large expert writing group for their enormous efforts to provide these new evidence-based recommendations and key messages on women's midlife health and menopause. In the time that has passed since publication of our last recommendations [4], new research into the health of midlife women and re-evaluation of existing data have allowed clinicians worldwide to gain more clarity into the role of MHT and alternatives, not only in the alleviation of troublesome menopausal symptoms but also in the prevention of diseases of aging.

The format of these new recommendations has evolved considerably since the last publication. The scope of the project was to provide guidance on the overall management of midlife health and menopause. The rigorous methodology required commencement with initial stakeholder surveys to define the key Population, Intervention, Comparison, and Outcome (PICO) questions, with topic-specific systematic reviews by two independent reviewers, where appropriate. This resulted in either an update or a complete rewrite of the previous text. The expert authors were asked to produce lists of recommendations, including the strength of recommendations and levels of evidence, good practice points (GPPs) and key messages.

This document represents the full online, updatable version of the IMS Recommendations and Key Messages on Women's Midlife Health and Menopause. In addition to the recommendations and key messages it contains the evidence behind the recommendations, references, tables, figures and supplementary materials. A detailed description of the methodology is provided in the next section.

It is hoped that this guidance will provide an overview that serves as a common platform on issues related to the various aspects of menopause, which can be easily adapted and modified according to local needs. Throughout the document, the term menopause hormone therapy (MHT) has been used to cover therapies including estrogens, progestogens and combined therapies. In view of national and regional variations in MHT availability, issues regarding specific MHT regimens and dosages are covered in detail in this online document, including a table of some treatment options (see Section 4a VMS: MHT Table 1). In line with research on the topic, terminology and discussion, the guideline is focused on women, but the IMS recognizes that there are individuals who are transgender or who do not identify with the terms used in the literature. Although the term 'women' is used, it is not intended to isolate, exclude or diminish any individual's experience nor to discriminate against any group.

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Methodology: searches / levels of evidence / grades of recommendations

This guideline was developed by a body of experts derived primarily but not exclusively from the IMS. Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and ClinicalTrials.gov databases were searched for relevant publications using the MeSH (Medical Subject Headings) and keyword search specific to each specialist area within menopause physiology and medicine. Information was also sourced from international guidance documents (consensus statement/position statement/clinical practice guideline) published by organizations such as the IMS, the European Menopause and Andropause Society (EMAS), The Menopause Society (TMS), the Endocrine Society, International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO). Particular attention was paid by the authors to new publications from 2016 onwards, the last time the IMS Recommendations were updated. Covidence, an online systematic review management tool, was used by the majority of authors for uploading and selecting relevant articles. The topics to be included were informed by an international survey of consumers and HCPs.

The quality of evidence and the strength of recommendations used in this 2025 guideline are based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) [1] and the Appraisal of Guidelines for Research & Evaluation II (AGREE II) [2] approaches. Article selection was based on predefined relevance criteria, including alignment with the clinical questions, population characteristics, study design, and reported outcomes. Following selection, the quality of original research was evaluated using the GRADE framework, which considers five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. In principle, recommendations should be derived from all available clinical practice guidelines. However, a full AGREE II assessment of each guideline is a resource-intensive process. Therefore, we predominantly relied on the most recent systematic reviews and on critical appraisals of menopause guidelines that had applied the AGREE II tool to ensure methodological rigour and evidence-based recommendations [3,4]. Compared to the 2016 IMS Recommendations, this update applies a more structured and transparent methodology by systematically incorporating these formal assessment tools—reflecting a notable shift toward greater methodological rigor.

Table 1 presents the definitions for levels of evidence (⊕⊕⊕⊕ [HIGH] to ⊕◯◯◯ [VERY LOW]) and grades of recommendations (A, B, C or D) used when assessing the quality of data and strength of recommendations in each section.

Each recommendation is based on both the level of evidence and other factors such as feasibility, values, preferences, and the balance of benefits and harms.

Areas where advice has been provided in the absence of good evidence, but based on extensive experience, are annotated as good practice points, indicated by (GPP).

Areas where evidence-based information has been provided as a statement, but not as a recommendation for management per se, are referred to as “Key Messages”. A Key Message (KM) may (or may not) have a level of evidence assigned but not a strength of recommendation.

KEY EXPLANATORY NOTES

Topics 27-29 were included due to interest ascertained in the healthcare professional and public stakeholder surveys, but it should be noted that the recommendations and key messages were derived from expert opinion as these topics were not amenable to formal systematic reviews of the scientific literature.

The ⊕ symbols (e.g., ⊕⊕⊕⊕) indicate the quality of the underlying evidence - how confident we are that the effect estimate is accurate.

The letter grades (A–D), on the other hand, represent the strength of the recommendation - that is, (how strongly the evidence is rated, or an intervention recommended). These grades are based not only on the quality of evidence, but also on factors such as feasibility, values, preferences, and the balance of benefits and harms (where consideration is being given to recommendation being implemented).

For example, if the level of evidence is high (⊕⊕⊕⊕), but the recommendation would be difficult to implement, for example, due to feasibility/resource restraints, then a lower strength of recommendation (B) can be given e.g. ⊕⊕⊕⊕ B

Conversely, if the level of evidence is moderate (⊕⊕⊕◯), but there is concern that failure to implement the recommendation would have a deleterious effect on health/quality of life, then a strong recommendation (A) can be given e.g. ⊕⊕⊕◯ A

Table 1: Quality of evidence and letter grades of recommendations.

Quality of evidence	Description	Examples	Grades of recommendation	Criteria
⊕⊕⊕⊕ HIGH	Further research is very unlikely to change our confidence in the estimate of effect.	High-quality systematic reviews and meta-analyses of randomized controlled trials or observational studies. Randomized clinical trials without serious limitations. Well-performed observational studies with very large effects (or other qualifying factors).	[A]	At least one systematic review and meta-analysis of randomized controlled trials, or randomized controlled trials, observational studies rated as ⊕⊕⊕⊕, and directly applicable to the target population and demonstrating overall consistency of results.
⊕⊕⊕◯ MODERATE	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Well-conducted systematic reviews and meta-analyses of randomized controlled trials or observational studies. Randomized clinical trials with serious limitations. Well-performed observational studies yielding large effects.	[B]	A body of evidence including studies rated as ⊕⊕⊕◯ directly applicable to the target population, and demonstrating overall consistency of results.
⊕⊕◯◯ LOW	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Systematic reviews and meta-analyses of randomized controlled trials or observational studies with serious limitations. Randomized clinical trials with very serious limitations. Observational studies without special strengths or important limitations.	[C]	A body of evidence including studies rated as ⊕⊕◯◯ directly applicable to the target population and demonstrating overall consistency of results.
⊕◯◯◯ VERY LOW	Any estimate of effect is very uncertain.	Randomized clinical trials with very serious limitations and inconsistent results. Observational studies with serious limitations. Unsystematic clinical observations (e.g., case series or case reports).	[D]	A body of evidence including studies rated as ⊕◯◯◯ directly NOT applicable to the target population and demonstrating overall inconsistency of results.
Good practice point/Expert opinion	Recommended best practice based on the clinical experience of the guideline development group.	Based on expert consensus where formal evidence is lacking.	-	Context-specific advice based on clinical expertise.

NB: The authors have strived for a consistent style of assessment and reporting by providing clear guidelines to the section authors at the beginning of the guideline process. However, due to the multi-author nature of this document, some variation in the consistency of data reporting and interpretation is inevitable.

A Publication Steering Committee (PSC) was set up consisting of the chair/lead author, representatives from the IMS secretariat, key authors, a librarian, a methodologist and a statistician to provide oversight of the process through regular meetings and issuing of guidance. Draft sections were submitted by the author(s) to lead reviewers selected from the PSC to provide peer review. The sections were then returned to the authors who answered any queries and returned the documents to the reviewers for final approval and inclusion in the manuscript. The final draft of the full text manuscript was reviewed by the PSC and the IMS Executive Committee and Board before uploading to the IMS Website.

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Sections: Full Text, Recommendations, Key Messages and References

The following sections include the full text, recommendations, key messages and references within each topic / key question. Whilst every effort has been made to provide the information in a standardised way, due to the multiauthor group that produced the information, there may be slight variation from section to section in the grammatic style and in the formatting of the guidance.

1. Midlife Body Changes (MBC) – Metabolic & Governing Principles

Weight gain is a common phenomenon among midlife women, with an average increase of 0.7 kg per year [1-9]. The relative contribution of chronological aging versus ovarian aging in midlife weight gain has long been debated, but the current evidence favors the predominant role of age-related decline in lean body mass and physical activity [10-12]. The universal decrease in muscle mass with age, resulting in a lower resting energy expenditure, and the commonly noted low levels of physical activity among midlife individuals, culminate in a reduction in the total energy expenditure and weight gain [1,13-23]. Although suboptimal dietary choices can result in weight gain, longitudinal studies have reported a lower, rather than higher, calorie intake among midlife women [6,24,25]. Additionally, the common menopause related symptoms, particularly vasomotor symptoms (VMS) and sleep disruption (due to VMS or otherwise), can also result in weight gain via complex mechanisms. Depressed mood, another common characteristic of the menopause transition, and weight gain commonly co-exist, sharing a bidirectional relationship [26-32].

Although the menopause-associated decline in estrogen is not the major driver for midlife weight gain, it is the main culprit for the characteristic body fat distribution changes after menopause [1]. Postmenopausal women tend to carry a greater proportion of their body fat in the abdominal (subcutaneous and visceral) distribution compared to their premenopausal counterparts, leading to central obesity and an increase in waist circumference [1,13,33,34]. Such an increase has been demonstrated even in women who maintain a normal body mass index through the menopause transition. The increase in visceral adiposity leads to an increased risk of diabetes, dyslipidemia, hypertension, and cardiovascular disease (CVD) which is the leading cause of mortality among postmenopausal women [35-39]. Additionally, even women with a normal body mass index (BMI) who have an elevated waist circumference have a comparable increase in cardiovascular mortality to women with an elevated BMI and waist circumference [40,41]. Thus, BMI alone without a measure of central obesity is not a satisfactory marker of adiposity-related risk of CVD and associated mortality in postmenopausal women.

Governing Principles

Calorie restriction, physical activity, and behavioral modification are the cornerstones of weight management [42-46], therefore, diligent attention to diet and physical activity can prevent weight gain in midlife women [47-52]. It is important to address individual and unique barriers to weight loss, including the influence of menopause-related symptoms. Appropriate management of vasomotor symptoms, sleep disruption, and mood disorders is key. Hormone therapy is the most effective intervention for the treatment of vasomotor symptoms and sleep disturbances in that context, but its use does not result in weight loss as such [53]. When choosing non hormone interventions for management of vasomotor or mood symptoms, it is important for healthcare professionals to be aware of the weight gain potential associated with certain medications, including gabapentin, clonidine, paroxetine, citalopram, amitriptyline, imipramine, mirtazapine, and clozapine. Weight-neutral or weight loss-inducing medications like escitalopram, sertraline, fluoxetine, venlafaxine, desvenlafaxine, fluvoxamine, fezolinetant, elinzanetant, and oxybutynin are preferable [54-56].

Anti-obesity medications are a consideration in women who meet prespecified BMI criteria. However, weight loss medications are expensive, may have side effects, and typically need to be used long term, potentially even lifelong [46].

Although menopause hormone therapy (MHT) does not have a direct impact on weight in midlife women, it does have a mildly favorable impact on body composition, including a decrease in abdominal adiposity and prevention of loss of muscle mass. However, these effects are likely related to the type of hormone therapy formulation and may be of minor clinical significance [57-60]. Additionally, hormone therapy use has also been associated with lowering of insulin resistance and reduction in the risk of diabetes [61]. However, MHT use is not indicated for its potential benefits on body composition and metabolic parameters in midlife women [53].

Recommendations and Key Messages

- Weight gain and body composition changes are common among midlife women. ⊕⊕⊕⊕ KM
- Midlife weight gain in women is mostly a result of chronological aging, and not menopause. ⊕⊕⊕◯ KM
- The aging-related decrease in total energy expenditure is the most important cause of midlife weight gain. ⊕⊕⊕⊕ KM
- Menopause related decline in estrogen is the major cause of an increase in abdominal adiposity among midlife women. ⊕⊕⊕⊕ KM
- Increased abdominal obesity, even in the presence of a normal BMI, confers a significant cardiometabolic risk in postmenopausal women. ⊕⊕⊕⊕ KM
- MHT effectively manages menopause symptoms but does not have a direct impact on body weight. ⊕⊕⊕⊕ KM
- Midlife women should be screened for weight gain, and appropriate counseling and management options should be offered. Behavioral modification, calorie restriction, and regular physical activity are the most important interventions for preventing and managing midlife weight gain. ⊕⊕⊕⊕ A
- Menopause symptoms, particularly vasomotor symptoms, sleep disturbances, and mood disorders, should be diligently managed to help improve adherence to healthy lifestyle measures for weight management. ⊕⊕⊕◯ B
- In the absence of a contraindication, MHT should be considered for the management of menopause symptoms in postmenopausal women, but MHT should not be used for weight management or for improving body composition. ⊕⊕⊕⊕ A
- Estrogen-based MHT can attenuate the body fat distribution changes of menopause and lower insulin resistance in a dose and formulation-dependent manner, but MHT use is not indicated for this reason. ⊕⊕⊕⊕ A
- Anti-obesity medications can be an important adjunct to lifestyle interventions for weight loss in midlife women who meet the BMI criteria for their use. However, these therapies can be expensive and typically require long-term use. ⊕⊕⊕⊕ A

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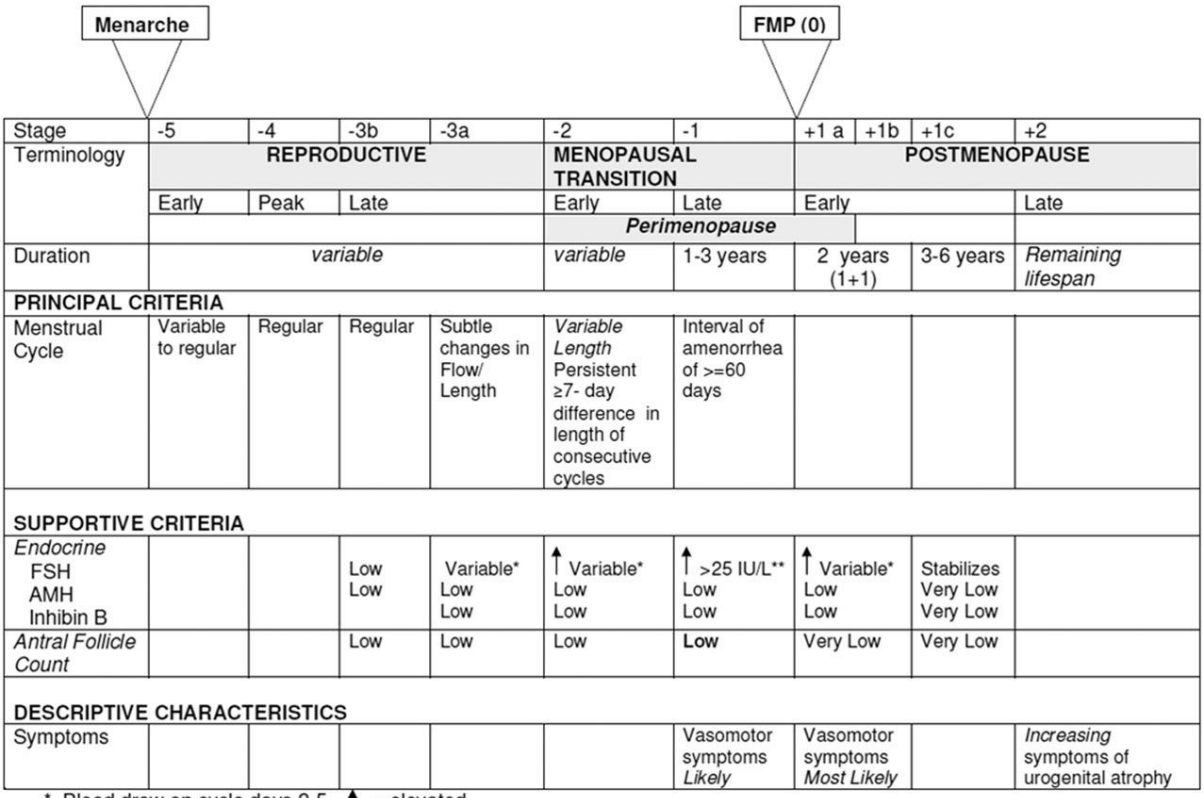
2. Diagnosis of Menopause including Stages of Reproductive Aging Workshop +10 (STRAW+10)

Menopause is the inevitable result of physiological age-related cessation of ovarian function that occurs between the ages of 45-55 years in high income countries Menopause may also result from iatrogenic secondary causes, such as surgery or be drug-induced. The diagnosis of menopause is a clinical assessment based on consensus by expert opinion. Accurate staging of reproductive aging is important from a clinical and research perspective. Presently, the gold-standard criteria endorsed by the IMS for staging reproductive aging remains the Stages of Reproductive Aging Workshop +10 (STRAW+10) [1] (see Figure 1). This has not been changed or updated since the 2016 recommendations.

Figure 1



	Menarche					FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

The principal criteria for diagnosis of menopause (STRAW+10) are based on menstrual cycle length.

Menopause is defined as the final menstrual period (FMP). Menopause is a retrospective clinical diagnosis, as the final menstrual period can only be defined if followed by 12 months of amenorrhea. The average age of menopause is about 51 years (UK and USA) but with significant ethnic and geographical variations [2].

Premature ovarian insufficiency (POI) is loss of ovarian activity before the age of 40 years and is characterized by hypergonadotropic hypogonadism with amenorrhea or irregular menstrual cycles for at least 4 months [3].

Early menopause is the cessation of ovarian function in women at the age of 40-44 years [3].

The **postmenopause** is the period following the FMP. The early postmenopause has an early phase divided into 1-2 years and 3-5 years and a late phase stretching over the remaining lifespan.

The **menopausal transition** starts at the end of the reproductive period and ends at the FMP, whereas **the perimenopause** starts at the end of the reproductive period and continues for 12 months after the FMP. The beginning of the menopause transition/perimenopause (early phase) is defined by the onset of variable menstrual cycle lengths of 7 days longer (or shorter) than the norm in consecutive cycles. The late menopause transition/ perimenopause is defined by periods of amenorrhea of >60 days. This precedes the FMP by about 1-3 years.

The reproductive period stretches from the menarche until the onset of early perimenopause and is characterized by regular menstrual cycles.

Supportive criteria (not essential for diagnosis):

Follicle-stimulating Hormone (FSH)

Blood should be drawn on day 2-5 of the menstrual cycle and analyzed according to the international pituitary standard. FSH values are stable during most of the reproductive period but become variable in the late reproductive period. FSH values start rising in the early perimenopause and reach levels of >25 IU/L in late perimenopause. They remain high in the postmenopause and stabilize after 2-3 years [4].

Anti-Müllerian hormone (AMH), inhibin B and antral follicle count (AFC).

AMH and inhibin B are blood markers of ovarian reserve. Both values decline in the late phase of the reproductive period with very low values in the postmenopausal period. Although they are not useful for diagnosing menopause, they are mainly used by infertility specialists to assess fertility potential. AMH has the potential to be used as an indicator of future age of menopause [5].

Specific cut-off values for AMH and inhibin B vary, given the lack of international standardization for those hormonal assays. AFC is an alternative ultrasonic imaging technique to determine ovarian reserve. It is, again, more useful in the determination of potential fertility than in the diagnosis of menopause.

Descriptive characteristics

According to the STRAW+10, vasomotor symptoms (VMS) occur from the late perimenopause but more recent studies indicate their earlier onset. The appearance of genitourinary symptoms is more likely in the late postmenopause [6].

Exceptions

The principal criteria based on menstrual changes cannot be used after hysterectomy, endometrial ablation, in case of polycystic ovary syndrome, progestogen releasing intrauterine system, hypogonadotrophic hypogonadism and POI. In such women, the supportive criteria should be used to determine reproductive stage. FSH>25 IU/L will generally be regarded as a diagnostic factor of menopause.

New evidence challenging the strategy of basing reproductive staging on menstrual characteristics as in STRAW+10

Several studies have shown that women in the late reproductive stage frequently experience symptoms similar to those reported by women designated as perimenopausal by STRAW+10 [7]. In the Women Living Better Survey, there was less than 10% difference in the prevalence of a range of symptoms between women in the late reproductive stage and perimenopause or early postmenopause [8]. This was further explored in the Australian Women's Midlife Years (AMY) Study, a large cross-sectional study of women aged 40-69 years [6]. Menopausal staging, by STRAW+10 (menstrual changes), and symptom severity as defined by the Menopause-specific Quality of Life (MENQOL) questionnaire were reported for 5509 women. The study demonstrated that women with regular cycles and changed flow (heavier or lighter periods) who reported VMS, classified as premenopausal by STRAW+10, had indistinguishable moderate to severely bothersome symptoms (for 28 of the 29 symptoms captured by MENQOL) from early perimenopausal women with VMS [6]. Similarly, women classified by STRAW+10 as late reproductive stage with no VMS were indistinguishable from early perimenopausal women with no VMS in their symptom profiles. Both groups with VMS (late reproductive and early perimenopause) had equally more severe symptom profiles than both groups with no VMS. These findings align with previous suggestions that the menopause transition commences before cycle length varies by 7 days [9-11], and support the conclusion that women with changed menstrual flow and VMS are likely to have entered the menopause transition [6].

Changes in the perimenopause

The impact of menopause has mostly been derived from studies comparing postmenopausal with premenopausal women, and from interventional studies in postmenopausal women. This had led to the broad conclusion that the over-riding impact of menopause is attributable to estrogen loss.

The longitudinal Study of Women Across the Nation (SWAN) has shown that estradiol blood levels are higher in the 5.5 years preceding menopause than in prior years in 45% of women [12]. Both SWAN and the AMY Study, have also shown that the majority of symptoms that characterize "menopause" emerge in the early perimenopause, with the onset of VMS often in the late reproductive years, before estrogen insufficiency occurs. Contrary to STRAW+10, both SWAN and the AMY Study have demonstrated the greatest reporting of VMS in the perimenopause [6,13]. Vaginal dryness, while often seen as a late symptom, also doubles in prevalence from premenopause by the late perimenopause [6]. Another consistent finding has been the greater reporting of memory complaints and brain fog during the perimenopause, with apparent resolution in most women after the final menstrual period [6,14]. Sexual desire and arousal dysfunction double in prevalence in the early perimenopause compared with premenopause [15], despite no evidence of a change in testosterone blood levels during the natural menopause transition [16-18].

SWAN has also demonstrated physiological changes, such as the accelerated accrual of visceral adipose [19] and increased total fat [20], commence in early perimenopause, but surprisingly do not accelerate after the final menstrual period when women are most severely estrogen depleted. Similarly, impaired endothelial function emerges in the early perimenopause [21]. In contrast, bone loss accelerates much closer to the final menstrual period, suggesting this more closely reflects estrogen loss [22].

These more recent findings indicate that the onset and peak of severely bothersome symptoms occur earlier than described by STRAW+10, and often in the context of relative estrogen sufficiency. Similarly, several physiological changes attributed to severe estrogen depletion emerge early in the menopause transition but do not significantly worsen when estrogen insufficiency becomes more severe and is sustained. This prompts caution in attributing the symptoms and health effects of the menopausal transition totally to estrogen insufficiency and the need for greater understanding of the changes occurring in the late reproductive years and early and late perimenopause. Such research will inform treatment approaches specific to the perimenopause. It is suggested that IMS takes the initiative in facilitating the process of revising STRAW+10 to determine the need for incorporation of the recent findings.

Recommendations and Key Messages

- Staging of reproductive aging should generally follow the STRAW+10 guidelines. GPP
- The diagnosis of menopause is a clinical diagnosis not dependent on special investigations. Supportive criteria described in STRAW+10 should be used for staging women who cannot be staged based on menstrual cycle characteristics. GPP
- Presently, the gold standard STRAW+10 criteria for determining menopause stage are based on menstrual cycle characteristics, including regularity and skipping of menstrual cycles, with blood tests for estradiol, follicle stimulating hormone (FSH) and/or anti-Müllerian hormone (AMH) conducted only as supportive criteria or as primary criteria for women who cannot otherwise be staged. ⊕⊕⊕⊕ A
- While the STRAW+10 guidelines, which rely on menstrual cycle irregularity, provide a useful clinical framework for identifying menopausal stages, the onset of menopausal symptoms is frequently earlier than suggested by STRAW+10, and VMS together with changed menstrual flow may signal the onset of the menopause transition. KM
- In women >40 years of age, the onset of moderately-to-severely bothersome VMS, regardless of menstrual cycle changes, should prompt a clinical evaluation of reproductive staging. ⊕⊕⊕◯ A
- The diagnosis of POI should be suspected in women younger than age 40 years with amenorrhea or irregular menstrual cycles for more than 4 months and with confirmed FSH values >25 IU/L. GPP
- Menopause between ages 40 and <45 years is termed early menopause. GPP

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3. Lifestyle, Diet, Exercise – Practical Advice

Lifestyle

Both scientific societies and governmental agencies endorse the promotion of a healthy lifestyle as a primary strategy to mitigate the burden of noncommunicable diseases (NCDs) and enhance overall health outcomes. A healthy lifestyle encompasses multiple protective behaviors, including the avoidance of toxic exposures (i.e. tobacco and excessive alcohol consumption, and illicit drug intake), the regular engagement in physical activity, and the adherence to a nutritionally balanced diet.

The promotion of a healthy lifestyle is currently a matter of public health and should be a comprehensive initiative that integrates educational institutions at all levels and actively involves key stakeholders such as the food industry, social media and advertising, medical institutions, healthcare professionals (HCPs), policymakers, and concerned individuals. Those who care for midlife women should assume a counseling role, offering informed guidance to support the adoption and sustained practice of health-promoting habits [1].

Obesity as a global health challenge

Obesity, defined as a body mass index (BMI) ≥30.0 Kg/m^2, has escalated to pandemic proportions, constituting a major global health challenge. According to the United Nations (UN), as of 2022, one in eight individuals was classified as obese, while 43% of the global population were overweight (25.0-29.9 Kg/m^2) [2]. These estimates may, however, underrepresent the true magnitude of the issue due to regional variations in BMI thresholds; for example, in Asian populations, the cutoff for overweight should be lowered to 23.0 kg/m^2 to more accurately reflect associated health risks [3].

In women, the menopausal transition is associated with increased total body fat and visceral adiposity, further complicating the maintenance of a healthy BMI and waist circumference (see section on midlife body changes). Obesity is associated with insulin resistance, which significantly increases the risk of cardiovascular disease, type 2 diabetes, and several cancers, including breast, colon, and endometrial malignancies [4,5]. Moreover, obesity may exacerbate menopausal symptoms, particularly vasomotor symptoms (VMS), although the strength and consistency of this association remain subjects of ongoing debate [6].

Diet

Diet represents a cornerstone of lifestyle interventions aimed at weight management and metabolic health. Epidemiological studies have identified key food groups that serve as fundamental components of a health-promoting dietary pattern. Vegetables, fruits, legumes, nuts, whole grains, olive oil, and fish have demonstrated protective effects on metabolic pathways and long-term weight regulation [7]. From a molecular level point of view, bioactive compounds have been identified as critical mediators of these health benefits. Among them, polyphenols and polyunsaturated fatty acids (PUFAs) are particularly notable for their protective roles in metabolic and cardiovascular health [8].

A variety of dietary patterns have been developed based on the recognized health-promoting properties of these foods. Beyond their established benefits, dietary recommendations must also account for practical considerations to facilitate large-scale implementation. This requires ensuring cultural adaptability across diverse global populations and aligning dietary guidelines with

sustainability principles. Therefore, contemporary nutritional policies should integrate global frameworks addressing climate change, such as those promoted by the EAT-Lancet Commission [9] and adhere to the regulatory directives of organizations such as the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) [10].

The Mediterranean Diet: a paradigm of evidence-based nutrition

The Mediterranean diet (MedDiet) is characterized by a food pyramid that prioritizes nutrient-dense and health-promoting food groups [11] (Figure 1). The broad applicability of the MedDiet facilitates its integration with local food availability and cultural traditions across diverse populations. Its health benefits are well documented, supported both by epidemiological data from populations traditionally adhering to this dietary pattern, and by a considerable body of clinical research.

From a nutritional standpoint, the MedDiet provides a balanced intake of macronutrients, including high-quality protein, healthy fats, and complex carbohydrates, along with essential micronutrients. Clinically, adherence to the MedDiet has been associated with a reduced risk of cardiovascular disease and the improvement of intermediate cardiovascular outcomes, such as blood pressure regulation, lipid profile optimization, obesity management, metabolic syndrome attenuation, and type 2 diabetes prevention. Additionally, emerging evidence highlights its potential benefits for cognitive function, mood regulation, specific cancer types, and overall mortality reduction [12].

Some studies have examined the impact of this type of diet on menopausal VMS. Vegan diets or, more generally, a higher intake of vegetables and fruits, appear to reduce VMS; however, the available studies are small in scale [13,14]. A reduction in VMS associated with the MedDiet has been reported in women participating in larger studies, such as the observational prospective Australian Longitudinal Study on Women's Health, which followed 6,040 women over nine years [15], or the Women's Health Initiative Dietary Modification study, a randomized controlled trial (RCT) that analyzed the effect of dietary intervention and weight change in 6,104 women and followed them for one year [16]. Nevertheless, the observed effect was modest.

Other dietary patterns with clinical relevance

Beyond the MedDiet, the Dietary Approaches to Stop Hypertension (DASH) diet warrants attention. Developed through a multicenter initiative led by the U.S. National Heart, Lung, and Blood Institute, the DASH diet shares substantial similarities with the MedDiet in terms of food group composition. However, its clinical evidence is primarily focused on intermediate cardiovascular outcomes, and the evidence on durable safety is lacking [17]. A key variant, the DASH-Sodium diet, incorporates sodium restriction and has demonstrated slightly superior efficacy in blood pressure reduction compared to the standard DASH protocol [18,19].

Intermittent fasting has gained popularity as a dietary strategy to promote weight loss and improve metabolic health [20]. Several variants exist, including alternate-day fasting and the 5:2 diet, among others. While no major safety concerns have been reported, this approach has been criticized, particularly due to a lack of long-term data, difficulties with adherence, and uncertainty about whether its effects are equivalent to those achieved through traditional calorie restriction [21,22].

In addition to supporting metabolic health, dietary strategies should also ensure sufficient intake of calcium and vitamin D. Scientific societies recommend a daily calcium intake ranging from 700 to 1,200 mg for women aged ≥ 50 years [23]. With advancing age, cutaneous synthesis of vitamin D from sunlight

declines, and sun exposure may entail dermatological risks. Consequently, the consumption of vitamin D-rich foods, such as fatty fish and egg yolks, is advised. Although no universally accepted optimal intake level for vitamin D exists, current guidelines suggest a daily intake of 400–600 IU for older adults, which may be increased to 800–1,000 IU in those with limited sun exposure [24]. Fortified foods, including milk, yogurt, and breakfast cereals, can serve as effective sources to help meet these requirements (for further information, see the section on osteoporosis). During midlife, women should aim for a daily protein intake of 1–1.2 g/kg body weight (=20% of total energy), ideally combined with regular resistance or weight-bearing exercise. This level supports maintenance and gain of skeletal muscle [25].

Diet and weight control

The MedDiet is considered a compelling option for sustained weight management, as it emphasizes the intake of foods with recognized weight-regulating potential [7]. Evidence suggests that MedDiet exerts a limiting effect on both overall body weight and central obesity [26]. Its impact on weight control has been found to be comparable to that of a vegetarian diet, provided both are adapted to be hypocaloric [27]. The use of olive oil as the principal dietary fat [28], combined with regular physical activity [29], may further potentiate these benefits.

Exercise during midlife

Physical activity or physical exercise in the aging population is generally associated with improved functional fitness and better quality of life. Similarly, exercise and physical activity in menopausal years can alleviate/reduce menopause related symptoms, especially vasomotor ones [30] as well as other menopausal outcomes [30,31]. Midlife women who are physically active display improved metabolic profile, muscle strength and function, cognition and overall better quality of life [32]. The benefits of exercise among older females are many and not only pertain to menopausal symptoms, but also to weight management and obesity prevention too. Weight loss reduces the risk of developing chronic conditions such as type-2 diabetes, cancer, and cardiovascular disease [31]. Although weight loss, as a consequence of increasing physical activity, may result in muscle loss, overall, exercise exerts positive effects on muscle, including: an increase of muscle mass, enhanced mitochondrial function, and improved insulin sensitivity [33]. These adaptations contribute to increased strength, endurance, and overall physical performance. Regarding bone health, exercise improves bone mineral density (BMD) and strength, reduces bone loss, and, together with strong musculature, reduces the risk of falls and fractures [34]. In addition, heart events, stroke, fractures as well as breast and colon cancers are significantly less frequent among physically active women. Overall, incorporating physical activity and exercise as a lifestyle modification during and beyond the menopause is an inexpensive and noncontroversial strategy to improve/maintain health of midlife and older women.

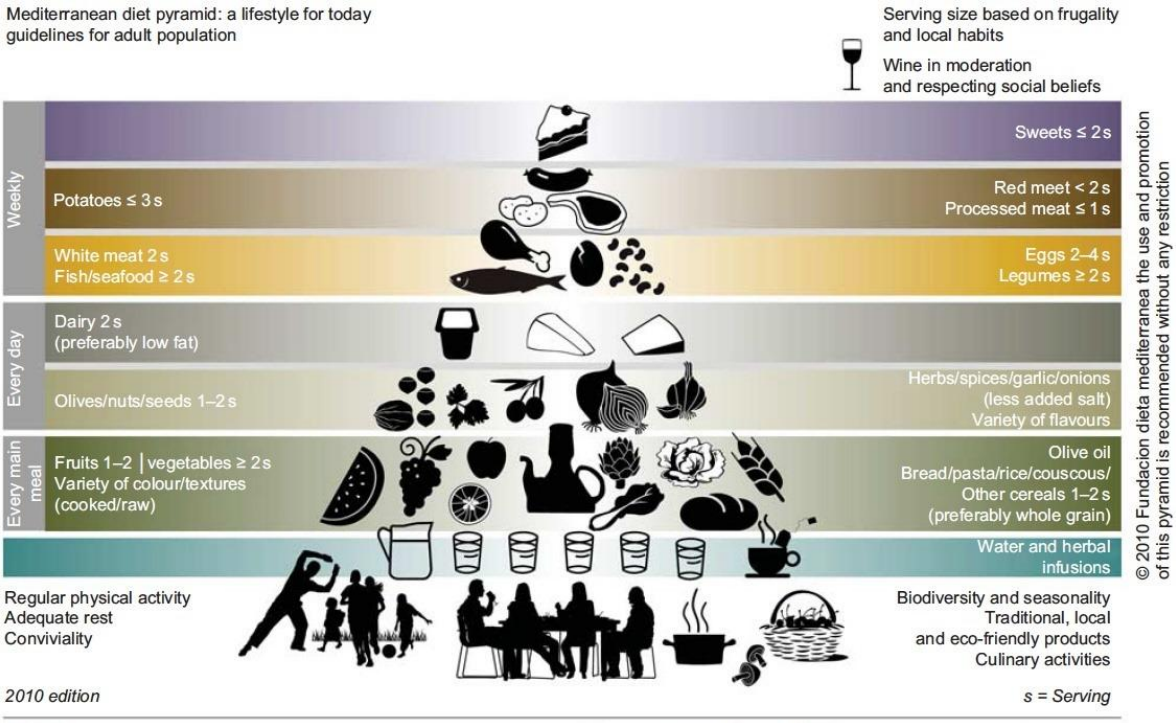
Physical activity and physical exercise are not the same; the first refers to the series of movements and actions normally performed on a daily basis (i.e. walking, housework or recreational activities), whereas physical exercise refers to a variety of planned, structured and repetitive body movements, which are performed in order to improve or maintain physical condition (i.e. aerobics, stationary cycling, weight lifting). The advantages of exercise clearly outweigh potential adverse effects; overall, greater activity is beneficial for menopausal women, although excessive or unbalanced exercise may be detrimental [31]. The Centers for Disease Control and Prevention (CDC) [35] and the World Health Organization (WHO) [36] recommend aerobic exercise, more specifically, at least 150 minutes of moderate-intensity aerobic exercise per week (e.g. brisk walking, cycling, or swimming), or 75 minutes

of vigorous-intensity aerobic exercise per week (e.g. running, jumping rope, or boxing). Adults can also engage in muscle-strengthening activities (weight-bearing exercise) that target all major muscle groups, such as legs, hips, back, chest, shoulders, and arms, at least twice a week (i.e. weightlifting, resistance band exercises, bodyweight exercises like push-ups, squats, and lunges).

Recommendations and Key Messages

- Obesity may exacerbate menopausal symptoms, particularly VMS, while diets rich in fruits and vegetables may help alleviate these symptoms; however, their effect is debatable. ⊕⊕⊕◯ B
- HCPs should be aware that weight loss of 5-10% is sufficient to improve many of the abnormalities associated with insulin resistance. ⊕⊕⊕⊕ B
- Key food groups such as vegetables, fruits, legumes, nuts, whole grains, olive oil, and fish are fundamental components of a health-promoting dietary pattern, offering protective effects on metabolic pathways and supporting long-term weight regulation. ⊕⊕⊕◯ B
- The Mediterranean diet appears to attenuate age-related increases in BMI and waist circumference, with more pronounced effects observed when combined with a hypocaloric diet and regular physical activity. ⊕⊕⊕⊕ B
- Adherence to a Mediterranean diet, as defined by the traditional food pyramid, has been associated with a reduced risk of cardiovascular disease ⊕⊕⊕⊕ A, improvements in intermediate cardiovascular outcomes, such as blood pressure, lipid profile, metabolic syndrome, and type 2 diabetes prevention ⊕⊕⊕◯ B, as well as benefits in cognitive function, mood regulation, the incidence of certain cancer types, and overall mortality reduction. ⊕⊕◯◯ C
- The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to improve lipid profiles and reduce blood pressure, although evidence supporting its long-term effects on clinical outcomes remains limited. ⊕⊕◯◯ C
- Regular exercise in midlife and older women is recommended to improve bone and muscle health, reduce cardiovascular and all-cause mortality, and decrease the risk of falls and fractures. ⊕⊕⊕⊕ B
- At least 150 min of moderate-intensity exercise per week is recommended as optimal; with two additional weekly sessions of resistance exercise providing further benefit. ⊕⊕⊕⊕ B
- The fitness of the older adult should be considered when recommending the intensity of aerobic activity. GPP
- Smoking should be stopped or avoided. ⊕⊕⊕⊕ A
- HCPs should inform women that a healthy lifestyle includes socializing and being physically and mentally active. GPP

Figure 1. The renewed pyramid representing the main components of the MedDiet and their relative intake frequency (reproduced with the permission of Dr. Lluís Serra-Majem) [10].



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4. a) VMS: MHT

Vasomotor symptoms (VMS), such as hot flushes and night sweats, are hallmark features of the menopausal transition and can markedly impair quality of life. They are also the most frequent reason women seek help from healthcare professionals (HCPs) [1].

VMS represent an exaggerated heat-dissipation response, characterized by episodes of heat (flushing) and sweating due to peripheral vasodilatation and increased skin blood flow. These events are triggered by a rise in core body temperature, primarily resulting from declining ovarian estrogen levels during the perimenopausal and menopausal transition [2].

Approximately 80% of women experience VMS, of whom around one in three will experience symptoms that are moderate to severe (defined as vasomotor symptoms that may disrupt daily activities and/or interrupt sleep) [3].

The median duration of VMS has been estimated between 2.6 [4] and 7.4 years [5], with the longest duration seen in women who report frequent VMS in early perimenopause [4,5]. In the Study of Women's Health Across the Nation (SWAN), African American women reported the longest duration of VMS compared to women of other ethnicities, with a median duration of 10.1 years, followed by Caucasian women and women of Asian descent [5].

In some women, VMS may persist into their sixties. A cross-sectional study found that VMS persisted beyond age 60 in 40.1%, with 6.5% reporting moderate to severe VMS [4]. A systematic review found that VMS persisted beyond the age of 65 in 20.9% to 45.1% of women, with 17.6% describing them as moderate and 2% as severe [6].

Increased frequency and severity of VMS have been associated with adverse cardiovascular risk profiles and early markers of subclinical cardiovascular disease, including greater carotid intima-media thickness, aortic calcification, and reduced brachial artery flow-mediated dilation (FMD), indicative of endothelial dysfunction [7,8].

The presence of VMS may also be associated with low BMD in postmenopausal women, although it does not seem to increase fracture risk [9,10].

Treating Vasomotor Menopausal Symptoms with MHT

MHT is the most effective treatment for VMS and should be offered to women with bothersome symptoms [11,12].

There are no reasons to place mandatory limitations on the duration of MHT. Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her HCP, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks [12].

MHT is an important first-line treatment for women with premature ovarian insufficiency (POI) and early menopause (EM) who may require MHT for symptom relief but also for primary prevention of diseases associated with these conditions [13].

MHT is particularly recommended for women experiencing distressing VMS and for the prevention of bone loss (particularly in women at a higher risk of osteoporosis), especially if they are younger than 60 years or who are within 10 years of their final menstrual period [11,12].

For women who initiate MHT more than 10 years from the menopause onset or who are older than age 60, the benefit- risk ratio may be less favorable, particularly for oral MHT, because of the greater absolute risk of coronary heart disease, thromboembolism and dementia; for this reason a decision to initiate treatment should include an individual assessment of risks and benefits [11,12].

Estrogen-only therapy (ET) is recommended for women following hysterectomy, while an estrogen-progestogen (EPT) combination is recommended for women with an intact uterus [11,12].

Both transdermal and oral estrogen routes are effective in treating VMS. Low-dose MHT is typically sufficient to relieve VMS in most women [14-16].

In cases where symptom control is inadequate, a stepwise approach involving dose escalation, a change in preparation or the route of administration (e.g. from oral to transdermal) may be considered to optimize therapeutic response while minimizing potential risks.

A significant reduction in VMS following treatment with MHT may be seen as early as two weeks after treatment initiation. However, this response is dose-related, and when low or ultra-low doses of MHT are used, significant reductions in symptoms may take longer to appear (3-4 weeks) and to achieve maximum symptom relief. Trials suggest that after 12 weeks of treatment, over 80% of women will have achieved a statistically significant reduction in frequency and severity of VMS compared to placebo [16,17].

Moderate to low doses of MHT have been shown to be sufficient to alleviate symptoms in over 80% of postmenopausal women; routinely measuring serum estradiol levels to determine the appropriate dose is generally not recommended [16-18].

Serum estradiol measurement may be helpful to monitor dose of MHT in women who, after 6-12 weeks of MHT treatment, report inadequate relief of symptoms, experience persistent adverse effects, and women with POI or early menopause particularly if there are concerns about inadequate symptom relief or inadequate bone mineralization [19].

Table 1 reflects various options for dose and routes of delivery of menopausal hormone therapy [20]. Studies have shown that the 52-mg LNG IUD provides sufficient endometrial protection against ultra-low to high doses of estrogen for up to 5 years in both peri- and postmenopausal women [21]. However, in some countries, the LNG IUD has only a 4-year license for progestogenic opposition of estrogen in hormone replacement therapy use [22,23].

Women should be counselled that there is no definitive, evidence-based guideline on the optimal method for discontinuing MHT, and VMS may recur in up to 87% of cases following the interruption of MHT [24,25]. A gradual dose reduction for 3 to 6 months has been suggested. Moreover, existing studies indicate that abrupt cessation may result in a recurrence of symptoms comparable to that observed with tapering doses [26,27]. Approximately 50% of women resume MHT following discontinuation, primarily due to the recurrence of VMS and a decline in overall well-being [28].

Contraindications to MHT include undiagnosed vaginal bleeding, estrogen dependent malignancy, active thromboembolic disease, acute liver disease, uncontrolled hypertension, acute cardiovascular events and porphyria cutanea tarda [25].

MHT should be used with caution in women with gallbladder disease, elevated triglycerides (oral MHT), hepatobiliary disease, migraine with aura, high risk of breast cancer, or high risk of cardiovascular disease [29].

Recent data show that when compared to placebo, both ET alone or EPT have been found to reduce weekly VMS symptom frequency by 75% (95% CI, 64.3-82.3) and significantly reduce VMS symptom severity (OR, 0.13; 95% CI, 0.07-0.23) [14-16].

In postmenopausal women, combined preparations of low-dose and ultra-low-dose of estrogen (1mg, 0.5 mg) and micronized progestogen (100mg) provided clinically meaningful improvements in the severity of hot flushes in the Clinical Global Impression (CGI) score by 0.525 and 0.350 points at week 4 and 0.775 and 0.225 points at week 12 [30,31].

Both oral conjugated estrogens (CEE) 0.45 mg daily and twice-weekly transdermal estradiol 50 µg patch, combined with cyclical micronized progesterone 200 mg for 12 days per month, have been found to significantly reduce VMS when compared to placebo. Moderate to severe hot flushes were reduced from 44% at baseline to 7.4% for transdermal MHT, 4.2% for oral CEE and 28.3% for the placebo group. There was no significant difference between the active treatment arms [32].

A network meta-analysis conducted by the National Institute for Health and Care Excellence (NICE) reported on the cost-effectiveness of using MHT for five years and concluded that both transdermal and oral MHT were effective options [11].

Data pooled from two double blind randomized controlled trials (RCTs) across Europe and China showed that ultra-low-dose continuous combined therapy (0.5mg estradiol / 5 mg dydrogesterone) significantly reduced the number of hot flushes when compared to placebo, with significant benefits seen at 4 weeks which continued to accrue over 12 weeks [17].

Both ultra-low dose and low dose continuous combined therapy (0.5mg estradiol / 2.5 mg dydrogesterone and 1mg estradiol / 5 mg dydrogesterone, respectively) effectively reduced the incidence of VMS when compared to placebo in postmenopausal Chinese women, irrespective of BMI [33].

Although the use of progesterone to improve sleep is “off label”, one study found that the use of oral 300mg micronized progesterone was associated with a 55% reduction in VMS and a significant improvement in sleep quality with no withdrawal-related VMS rebound [34].

Estetrol (E4), a native estrogen in the fetal liver thought to have selective tissue actions, in an oral dose of 15mg daily has been shown to reduce both the frequency and severity of moderate to severe hot flushes in postmenopausal women. Hot flush frequency was reduced by 66% at week 4 and 82% at week 12 compared to placebo (49% at week 4, 65% at week 12) [35].

Randomized placebo-controlled trials of a combination of conjugated estrogens 0.45mg and bazedoxifene 20mg, known as a tissue selective estrogen complex (TSEC) found that the combination significantly reduced the frequency and severity of VMS compared to placebo at week 4. At week 12,

hot flush frequency was reduced by 74% and hot flush severity by 37%, with benefits persisting for 24 months [36,37].

Tibolone, a selective tissue estrogenic activity regulator (STEAR) has been shown to significantly reduce VMS compared to placebo in postmenopausal women (OR 0.33, 95%CI 0.27-0.41). Whilst greater than placebo, this effect was less than that seen with standard dose MHT [38].

Recommendations and Key Messages

- HCPs should inform women that VMS, such as hot flushes and night sweats, are hallmark features of the menopause transition and menopause, and can markedly impair quality of life. ⊕⊕⊕⊕ A
- MHT is the most effective treatment for VMS. Where available, it should therefore be offered to women with bothersome VMS who do not have significant contraindications or are not MHT averse. ⊕⊕⊕⊕ A
- When used for the treatment of VMS, MHT is typically recommended to women less than 60 years old or within 10 years of menopause after a full evaluation of benefits and risks. ⊕⊕⊕⊕ A
- HCPs should be aware that both transdermal and oral estrogen routes are effective in treating VMS, with low to moderate doses of MHT alleviating symptoms in over 80% of postmenopausal women. ⊕⊕⊕⊕ A
- Where symptom control is inadequate with low to moderate doses, a stepwise approach involving appropriate investigation, dose escalation, a change in preparation or the route of administration may be considered to optimize individual therapeutic response, whilst reducing potential risks. GPP
- Estrogen-only therapy (ET) is recommended for women without an intact uterus, while an estrogen-progestogen (EPT) combination is recommended for women with an intact uterus. ⊕⊕⊕⊕ A
- Tibolone, a selective tissue estrogenic activity regulator (STEAR) has been shown to significantly reduce VMS compared to placebo in postmenopausal women (OR 0.33, 95%CI 0.27-0.41). ⊕⊕⊕⊕ A
- Estetrol (E4) (a native estrogen in the fetal liver thought to have selective tissue actions), in an oral dose of 15mg daily has been shown to reduce both the frequency and severity of moderate to severe hot flushes in postmenopausal women. At the time of writing, this had not yet received marketing approval. ⊕⊕⊕⊕ A
- HCPs should be informed that routine measurement of serum estradiol levels to determine the appropriate dose of MHT is generally not recommended. However, serum estradiol level measurement may be helpful in women who report inadequate symptom relief, persistent adverse effects and women with POI or early menopause. GPP
- Women should be counselled that there is no definitive, evidence-based guideline on the optimal method for discontinuing MHT, and VMS may recur in up to 87% of cases following the discontinuation of MHT. ⊕⊕◯◯ C

Table 1. Summary of menopause hormone therapy options. ***Modified with permission from Panay, N et al. 2020 [20].***

MHT type	***Sequential combined MHT***		***Continuous combined MHT***	
Per 24 hours or day	*Low/standard doses*	*High doses*	*Low/standard doses*	*High Doses*
Estrogen type				
Patch (transdermal, µg/24h	**25–50**	**75–100**	**25–50**	**75–100**
Gel sachet (transdermal, mg)	**0.5–1.5**	**2.0–3.0**	**0.5–1.5**	**2.0–3.0**
Gel pump (1 metered dose = 0.75 mg)	**1–2**	**3–4**	**1–2**	**3–4**
Transdermal spray (1.53mg per spray)	**1-2**	**3-4**	**1-2**	**3-4**
Oral (mg)	**1.0–2.0**	**2.5–4.0**	**1.0–2.0**	**2.0–4.0**
Conjugated Equine Estrogens CEE (mg)	**0.3-0.625**	**0.9-1.25**	**0.3-0.625**	**0.9-1.25**
Progestogen				
Micronized progesterone (oral/per vagina, mg)	**100–200**	**≥ 200 (e.g. 300–400)**	**100**	**≥ 200**
Dydrogesterone (oral, mg)	**10**	**20**	**5.0**	**10**
Medroxyprogesterone acetate MPA (oral, mg)	**5.0*-10**	**10-20**	**2.5**	**5.0**
Norethisterone acetate (oral, mg)	**2.5–5.0**	**2.5–10**	**1.25–2.5****	**2.5-5.0**
Levonorgestrel intrauterine system (LNG IUD)	**20 µg/day sufficient for low/standard and POI doses (52mg LNG IUD)**			
Estrogen/progestogen fixed dose combined preparations				
E2/micronized progesterone (oral, mg)	**n/a**	**2.0-3.0/200-300**	**1.0–2.0/100–200**	**3.0–4.0/300–400**
E2/norethisterone acetate (transdermal) (µg)	**25–50/85–170**	**75–100/255–340**	**25–50/85–170**	**75–100/255–340**
E2/dydrogesterone (oral, mg)	**1.0–2.0/10**	**2.0/10**	**0.5–1.0/2.5–5.0**	**3.0–4.0/7.5–10**
E2/norethisterone acetate (oral, mg)	**1.0–2.0/1.0**	**3.0–4.0/2.0–4.0**	**0.1–2.0/0.5–1.0**	**3.0–4.0/1.5–2.0**
CEE/MPA	**0.625/5.0**	**n/a**	**0.3-0.625/1.5-5.0**	**n/a**
Fixed Dose Regimes				
Tissue Selective Estrogen Complex (TSEC)	Conjugated Equine Estrogens 0.45 mg Bazedoxifene 20 mg			
Selective Tissue Estrogenic Activity Regulator	Tibolone 2.5 mg			

Notes

- The table does not show all available options globally. Some regimens are achieved off label on first principles by halving/doubling/combining regimens especially for the fixed dose combined regimens.
- Variation globally as to what doses perceived as low, medium, and high, e.g. North America 0.5 mg E2 is low dose, 1 mg E2 is standard dose, and 2 mg E2 is high dose.
- Sequential regimens require 12-14 days progesterone/progestogen per cycle for endometrial protection – this may need modification depending on tolerance.
- Endometrial safety is less assured with micronized progesterone used for > 5 years.
- Progesterone/progestogen doses shown are the minimum effective for endometrial protection given current data.
- Endometrial safety data are lacking for the minimum effective dose of progestogen/progesterone with higher estrogen doses.

* The licensed dose for sequential MPA is 10mg; 5mg is a compromise low dose for progestogen intolerant patients on low dose estrogen

** A 1 mg dose of norethisterone acetate is adequate for standard-dose continuous combined HT but is only available in a fixed dose combination with E2, hence 1.25–2.5 mg doses (¼ to ½ of a 5 mg tablet).

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4. b) VMS: Non-Hormonal Pharmacological

Vasomotor symptoms (VMS), which occur in 75 to 80% of menopausal women [1] and last for a median duration of 7.4 years with variations observed across ethnic groups [2], have been shown to be bothersome and disruptive. Moreover, they are associated with adverse health consequences, affecting cardiovascular and cognitive systems, as well as with the increased risk of bone loss and osteoporosis [3-9].

Hormone therapy (HT) remains the gold standard for treatment of VMS with an average of 75% reduction in hot flush frequency compared to placebo [10]. However, not all menopausal women are candidates for HT or choose to take it, either due to fear of cancer or personal preference. Contraindications to HT include unexplained vaginal bleeding, history of estrogen sensitive cancers (e.g., breast, endometrium), recent, or history of stroke, history of or at high risk of thromboembolic disease, liver disease, migraine headaches with aura, uncontrolled hypertension, myocardial infarction, coronary heart disease and porphyria cutanea tarda. Risks are increased with later age of initiation or longer durations, and health risks in general increase with age [11]. Medical comorbidities and individualized risks and benefits need to be taken into account in decision making about the use of menopausal hormone therapy (MHT) or alternatives [12]. Therefore, effective and safe non-hormonal therapies are needed.

Need for placebo-controlled trials

A placebo effect has been consistently observed across all randomized, placebo-controlled trials evaluating treatments for moderate to severe VMS. A meta-analysis of 117 studies has shown a mean reduction in VMS frequency of 5.44 episodes per day with placebo (95% CI, –5.81 to –5.07) at 12 weeks, with a comparatively smaller improvement in VMS severity –0.36 (95% CI, –0.46 to –0.27). This underscores the importance of placebo-controlled trials when assessing the efficacy of new therapies [13].

Neurokinin Receptor Antagonists (NKTs)

In the past few years, the pathophysiology of VMS has been expanded to include kisspeptin, neurokinin B, and dynorphin neurons (KNDy) which play a role in thermoregulation and are influenced by declining serum estrogen levels [14]. A new class of therapies, neurokinin receptor antagonists, have been developed, which block or modulate the binding of neurokinin B to hypothalamic KNDy neurons, and thus reduce their effects on the thermoregulatory pathway [15], leading to a reduction in the frequency and severity of hot flushes.

The first neurokinin receptor antagonist to become FDA approved, with multiple key government approvals, and commercially available was fezolinetant, a neurokinin 3 (NK3) receptor antagonist. Three phase 3 studies (in SKYLIGHT trials 1, 2, and 4) have demonstrated the efficacy, safety, and tolerability of fezolinetant [16-18]. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) confirm significant reductions in both frequency and severity of hot flushes with rapid onset within a week [19]. At 45 mg oral daily dosing, fezolinetant reduced VMS frequency by more than 50% compared with placebo (on average 2 to 3 fewer VMS episodes per day sustained through week 52) [16-18]. A systematic review and network meta-analysis by Morga [19], which included data from the pooled phase 3 fezolinetant trials and comparators, demonstrated that fezolinetant 45 mg

significantly reduced the frequency of moderate to severe VMS events per day compared with evaluated non-hormonal therapies and was only less effective than 2.5 mg of tibolone and conjugated estrogens 0.625 mg/bazedoxifene 20 mg. There are no head-to-head comparisons to tibolone, hormone therapy or other NKTs.

Common side effects of fezolinetant in the clinical trials included headache, nausea, abdominal pain, and gastrointestinal issues. In a pooled analysis of clinical trial data, Kagan [20] found that approximately 2.3% of patients receiving fezolinetant 45 mg experienced transaminase elevations. These findings led to the conclusion that monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be recommended during treatment. In the US, due to a severe case of liver toxicity at 40 days, liver tests are now recommended at baseline and months 1, 2, 3, 6, and 9. In addition, caution needs to be exercised if given with concomitant CYP1A2 enzyme inhibitors, which could increase the potency of fezolinetant.

Contraindications include cirrhosis, severe renal impairment, and the concomitant use of CYP1A2 inhibitors (such as specific SSRIs (like fluvoxamine), fluoroquinolone antibiotics, and some estradiol formulations), which may increase the systemic exposure and potency of fezolinetant. Caffeine consumption was not limited in participants of fezolinetant clinical studies.

A second neurokinin receptor antagonist, elinzanetant, administered orally at a dose of 120 mg, acts as a dual receptor antagonist in both the neurokinin-1 and neurokinin-3 receptors (NK1, NK3). RCTs have demonstrated significant reductions in both the frequency and severity of hot flushes [21,22], including the breast cancer population with VMS due to endocrine therapy [23]. Rapid onset was seen with one week with sustained efficacy to 52 weeks in Oasis 3 [22]. Clinically meaningful improvements in sleep and quality-of-life measures were also seen in OASIS 1, 2 and 3, felt to be due to the effect on NK1 receptor antagonism, working through substance P. Thus, in addition to rapid reduction of VMS, elinzanetant holds promise of improving sleep and menopause related quality of life through its dual neurokinin receptor effects.

Elinzanetant has multiple key government approvals and is approved in Europe-EU for both moderate-to-severe VMS associated with menopause or caused by adjuvant endocrine therapy related to breast cancer [24].

A systematic review and meta-analysis by Menegaz de Almeida [25] of 7 RCTs with 4,087 participants found that both fezolinetant and elinzanetant were associated with significant reductions in VMS frequency and severity, with elinzanetant showing a greater effect size and improved sleep quality. Another systematic review and meta-analysis [26] evaluated ten studies with 4663 participants and found that both elinzanetant and fezolinetant achieved >50% reductions in VMS. Elinzanetant demonstrated a comparatively greater effect as it was additionally associated with improvements in menopause-specific quality of life.

Both fezolinetant and elinzanetant are being tested in breast cancer survivors or those at high risk of breast cancer. Both agents have demonstrated efficacy in data presented at scientific society abstracts, with complete data for elinzanetant recently published [23]. Elinzanetant is currently being tested for its effects on sleep in participants experiencing menopause-related sleep disturbances (NIRVANA phase 2).

Q-122 is a novel oral, non-hormonal therapeutic agent that has shown promise in early clinical trials. It reduces the frequency of neuronal activation events mediated by KNDy neurons but does not act as a neurokinin-3 (NK3) receptor antagonist. A 28-day phase 2 multinational clinical trial (Q-122 n=65 and placebo n=66) in breast cancer patients showed promise for further development [27].

Additional pharmacologic non-hormonal therapies for VMS

Pharmacologic non-hormonal therapies shown effective in non-head-to-head randomized placebo controlled clinical trials (RCTs) include selective serotonin and norepinephrine receptor inhibitors (SSRIs, SNRIs), gabapentin, and oxybutynin. The neurokinin receptor antagonists appear more effective at relieving hot flush frequency and severity and are closer to the effectiveness of HT. However, there are no head-to-head trials. A few head-to-head trials have compared either SSRIs or SNRIs with estrogen for VMS. These studies demonstrated comparable reductions in hot flush frequency; however, they were not conducted under the FDA's threshold requirement of ≥50 moderate to severe hot flushes per week. SSRIs and SNRIs have shown benefit when compared to oral estrogen with escitalopram 10-20 mg per day compared to low dose 0.5 mg oral estradiol and venlafaxine 75 mg [28].

A 2006 systematic review and meta-analysis of non-hormonal pharmacologic agents in randomized clinical trials (RCTs) included 10 trials of antidepressants, 10 trials of clonidine, and 6 trials of other prescribed medications [29]. It was demonstrated that the number of daily hot flushes decreased compared with placebo in meta-analyses of 7 comparisons of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (mean difference, -1.13; 95% confidence interval [CI], -1.70 to -0.57), 4 trials of clonidine (-0.95; 95% CI, -1.44 to -0.47), and 2 trials of gabapentin (-2.05; 95% CI, -2.80 to -1.30). Efficacy evidence was limited due to small numbers of trials, deficiencies in trials, and lack of comparative trials or head-to-head trials. Treatments included were the following: paroxetine (10 mg/d, 12.5 mg/d [controlled release], 20 mg/d, 25 mg/d [controlled release]), venlafaxine extended release (37.5 mg/d, 75 mg/day 2 trials), fluoxetine (20 mg/d), and citalopram (20 mg/d) with support for use of SSRIs, SSNRs, clonidine and gabapentin based on a small number of fair-good trials. Clonidine reported inconsistent results but has been shown to be superior to placebo in RCTs. The two trials of gabapentin (900 mg/d) indicated a reduction of 2 hot flushes per day compared with placebo, without benefit at 300 mg [29].

Large, randomized double-blind placebo-controlled trials have shown a reduction of hot flushes with the use of paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, and duloxetine. SNRIs have been shown to reduce hot flushes by up to 50% in the affected patients. Neither sertraline nor fluoxetine have demonstrated consistent efficacy in alleviating these symptoms [30].

The above listed medications may also improve mood, some may improve arthralgias, although low doses are typically used for VMS relief. A systematic review by Azizi on the safety and efficacy of SSRIs and SNRIs included 27 RCTs (out of 36) and, for SSRIs, demonstrated higher efficacy of escitalopram, paroxetine, and fluoxetine, with limited numbers or inconsistent results for sertraline, citalopram, and fluvoxamine [31]. Regarding SNRI class, significant efficacy was seen with venlafaxine and desvenlafaxine, with a limited number of available trials of duloxetine. The review highlighted the need for further, high quality, longitudinal studies to determine best treatment choices.

Adverse events

While low doses of SSRIs and SNRIs improve VMS, higher doses improve mood symptoms but may be associated with weight gain [32], VMS or sweating. This is seen more often with SNRIs because of their binding to norepinephrine [33]. In addition, abrupt interruption of SSRIs and SNRIs may lead to severe withdrawal symptoms. Too much serotonin inhibition has been associated with serotonin syndrome - a rare, serious, and potentially life-threatening condition resulting from excessive serotonergic activity in the central nervous system. SNRIs may increase blood pressure, thus, in patients with hypertension a cautious use is recommended. Venlafaxine is the most extensively studied SNRI in combination with tamoxifen and is not believed to interfere with the CYP2D6 enzyme activity. Duloxetine, although less extensively studied, demonstrates a moderate effect on the CYP2D6 enzyme. Fluoxetine and sertraline are generally not recommended for VMS reduction due to inconsistent data regarding their efficacy in hot flush frequency and severity reduction. In addition, sertraline has a moderate effect on the CYP2D6 enzyme. Citalopram and escitalopram may cause QT prolongation [34,35].

SSRI: Paroxetine

Paroxetine mesylate 7.5 mg was the first US FDA-approved nonhormone medication for moderate to severe menopausal VMS. A systematic review and meta-analysis evaluating low-dose paroxetine (7.5–12 mg) included nine trials, of which five RCTs comprising 1,482 participants (738 receiving paroxetine and 744 receiving placebo) were eligible for analysis [36]. Hot flush episodes were significantly reduced for those in the paroxetine treatment arm over placebo (mean difference (MD) −7.97 [−10.51, −5.92] episodes/week, regardless of the cause of menopause (natural or surgical). The main adverse events seen in a review of paroxetine at higher doses of nausea or dizziness [37] were not seen in this review. Low dose paroxetine may benefit sleep and mood due to the overlap of VMS, but this was not shown in the meta-analysis. Two RCTS of 24 weeks of 7.5 mg paroxetine methylate compared to placebo found a reduction in moderate to severe VMS through 24 weeks, with a greater proportion of responders in the treated group, and a low incidence of adverse events and no discontinuation-emergent symptoms [38].

SSRI: Escitalopram

In a systematic review by Azizi, six studies assessed the efficacy of escitalopram in the treatment of VMS, with five showing a significant reduction in frequency and severity of VMS with escitalopram compared to the placebo [31]. The most common side effects reported by the participants were dizziness or lightheadedness, vivid dreams, nausea, and excessive sweating. One RCT showed escitalopram 10-20 mg was associated with fewer and less severe menopausal hot flushes at 8 weeks of follow-up and improved menopause related quality of life [39]. The 8-week reduction in VMS frequency from baseline compared to placebo was similar for escitalopram 10-20 mg at -1.4 per day (95% confidence interval [CI] -2.7 to -0.2), low-dose oral estradiol 0.5 mg at -2.4 (95% CI -3.4 to -1.3), and 75 mg of venlafaxine at -1.8 (95% CI -2.8 to -0.8) [28].

SNRI: Venlafaxine and Desvenlafaxine

Five studies have reported that desvenlafaxine at varying doses was an effective non-hormonal drug in the treatment of menopausal hot flushes [31]. Lower doses of venlafaxine of 37.5 mg and 75 mg are generally recommended to decrease side effects such as dry mouth, nausea, restlessness, and insomnia. Two RCTs evaluated desvenlafaxine 150 mg for moderate to severe VMS [40,41]. In a 12 week trial, a rapid reduction of moderate to severe hot flushes was seen at 4 weeks and maintained to 12

weeks [41]. In the second 52 week trial, frequency and severity were significantly reduced by week 12 [40]. A mild increase in blood pressure was reported. Caution is recommended in older women due to the risk of hyponatremia and hypotension, and treatment discontinuation should include a slow taper over several weeks.

Gabapentin

Gabapentin and pregabalin have been shown in RCTs to reduce hot flush frequency (54%) and hot flush composite score by 31-51%. In a systematic review and meta-analysis of 19 RCTs and 2 randomized crossover trials of 3519 participants it has been found that gabapentin reduced hot flush frequency compared to placebo (mean difference, -1.62, 95% confidence interval, -1.98 to -1.26 after 4 weeks; mean difference, -2.77, 95% confidence interval, -4.29 to -1.24 after 12 weeks) [42]. Yoon, in a meta-analysis of 7 RCTS comparing gabapentin to placebo, found a significantly greater reduction in frequency, duration and composite score in women undergoing gabapentin treatment, however, more adverse effects were also seen compared to placebo [43].

Gabapentin nighttime administration (starting dose of 100-300 mg) is recommended to improve nocturnal sweats and sleep quality, as well as to avoid daytime fatigue, as drowsiness is the most common side effect. If tolerated, doses up to 900 mg of gabapentin are commonly used (600 mg at night and 300 mg during the day. Side effects include dizziness, loss of coordination, weight gain, swelling, and gastrointestinal issues [43]. The evidence for treatment of VMS with pregabalin is limited but warrants further investigation.

Oxybutynin

Oxybutynin is an anticholinergic, antimuscarinic therapy effective for urinary urgency, overactive bladder, and hyperhidrosis. Two RCTs have shown that oxybutynin is effective at reducing hot flush frequency, in a range of 70-86%, and thus may be a good choice for women with overactive bladder symptoms and VMS [44, 45]. These RCTS have demonstrated that oxybutynin doses from 2.5 mg or 5 mg twice daily [44] and up to 15 mg extended release daily [45] significantly improved moderate to severe VMS in postmenopausal women. Adverse events of oxybutynin are usually dose-dependent and most commonly include a dry mouth and urinary retention, nausea and constipation, dizziness, and vision changes. It is not recommended for women aged 65 or older, as anticholinergic therapies have been associated with cognitive issues, risk of dementia, and delirium [46].

Clonidine

Although RCTs, including those involving women receiving tamoxifen, have demonstrated that clonidine can reduce the frequency of hot flushes, its use is generally not recommended due to its relatively limited efficacy and a higher incidence of adverse effects, such as hypotension, dizziness, sedation, and the potential for rebound hypertension or withdrawal symptoms upon discontinuation [30]. It can be considered if blood pressure control and improvements in hot flushes are desired but not recommended for ages over 65 due to side effects [30].

Suvorexant

Suvorexant is a dual orexin receptor antagonist evaluated in a small RCT of 56 women [47] with chronic insomnia and nighttime VMS, which was well tolerated and appeared to decrease nighttime VMS and VMS associated insomnia disorder. Despite promising initial outcomes, further testing is needed.

Stellate ganglion block

Stellate ganglion blockade involves the injection of an anesthetic agent at the lower cervical or upper thoracic region, where the stellate ganglion is located (C6-T2) region of the anterior cervical spine. VMS reduction has been observed in RCTs in women with and without breast cancer, although the mechanism of action of the blockade on VMS has not been identified [48]. Due to the potential risks related to the procedure and the need for skilled operators, larger trials of effectiveness and safety are needed.

Women with a history of breast cancer, or at high risk of breast cancer

Women with a history of breast cancer (or at high risk) represent a significant number of patients/survivors with unmet needs, where non-hormonal treatments are often used for the treatment of VMS.40 to 50 percent of breast cancer women undergoing chemotherapy experience premature menopause symptoms, including VMS, and endocrine therapies such as tamoxifen and aromatase inhibitors may induce or aggravate VMS [49]. Paroxetine salt 7.5 mg oral daily is an FDA approved non-hormonal therapy shown in RCTs to be more effective than placebo in participants without breast cancer.

Rada in a 2010 Cochrane review, analyzed sixteen RCTs of hot flushes in women with a history of breast cancer with six studies on SSRIs and SNRIs, two on clonidine, and one on gabapentin, with low or moderate risk of bias [50]. The SSRIs and SNRIs, clonidine, and gabapentin reduced the number and severity of hot flushes, while no benefit was seen in the one clinical trial on Vitamin E. Side effects were described as inconsistently reported.

Certain SSRIs, such as paroxetine and fluoxetine, are more potent inhibitors of p450 CYP2D6. As CYP2D6 is responsible for the metabolic conversion of tamoxifen to its active metabolite, endoxifen, concurrent use of these SSRIs is not recommended, as it may reduce tamoxifen bioavailability and therapeutic efficacy [51]. In addition, concern has been raised regarding the potential association between SSRI use, CYP2D6 inhibition, and cancer recurrence or mortality, but studies have reached inconsistent conclusions [52]. If an SSRI/SNRI is to be used for breast cancer survivors, compounds that interfere less with tamoxifen metabolism, such as venlafaxine and citalopram, are preferred. SSRIs do not interfere with the action of aromatase inhibitors and can be used safely in women receiving these drugs. Side effects of medications need to be considered. The most common adverse effects of SSRIs and SNRIs are gastrointestinal disturbances, including nausea, sleep disruption, weight changes, and effects on sexual function. As demonstrated in an RCT, the low dose of 7.5 mg of paroxetine mesylate was not associated with weight gain or loss of libido up to 24 weeks [36]. Although not approved (except in Europe) for use in women on endocrine therapy for breast cancer with bothersome VMS, elinzanetant, a dual NK1, NK3 receptor antagonist, has shown promise at 52 weeks in relieving hot flushes [23] with the most common side effects of headaches, fatigue, and somnolence, and no substantive increased risk of liver toxicity. Fezolinetant, an NK3 receptor antagonist approved for the treatment of VMS, is in testing for women with breast cancer on endocrine therapy (see Clinicaltrials.gov ID NCT06440967).

NKT should be considered as a preferred evidence-based, effective non-hormonal option because of the high quality of the RCT data supporting their efficacy; their mechanism of action, which directly targets the brain areas responsible for generating VMS; their rapid and demonstrated sustained

efficacy of 60-70%, with multiple key government approvals deeming them safe and effective. Both have shown rapid onset of action at one week, and sustained efficacy and safety at 52 weeks.

Recommendations and Key Messages

- MHT remains the gold standard treatment for menopausal hot flushes for healthy symptomatic menopausal women when initiated close to menopause. However, for women with health conditions considered strong contraindications to HT or, who cannot, or choose not to take MHT, non-hormonal pharmacologic therapies are needed. KM
- A new class of neurokinin-targeted therapies, which are non-hormonal treatments, offers an evidence-based approach for effective treatment. Neurokinin receptor antagonists reduce the frequency and severity of VMS in postmenopausal women by modulating kisspeptin, neurokinin B, and dynorphin neurons (KNDy) in the hypothalamus, with effectiveness appearing slightly less than that of MHT. KM
- NKT should be considered as a preferred evidence-based, effective non-hormonal option because of the high quality of the RCT data supporting their efficacy. KM
    - Fezolinetant is an NK3 receptor antagonist, shown to be effective in phase 3 clinical trials, with multiple key government approvals for VMS and in testing in women with breast cancer. ⊕⊕⊕⊕ A
    - Elinzanetant is a dual NK1 and NK3 receptor antagonist, shown to be effective in phase 3 clinical trials, with multiple key government approvals for VMS and shown to be effective for endocrine therapy associated VMS in women with breast cancer. ⊕⊕⊕⊕ A
- RCTs of non-hormonal pharmacologic agents shown to be effective in reducing VMS due to menopause, but without government approval for VMS (except for paroxetine salt 7.5mg in the USA), include selective serotonin and norepinephrine receptor inhibitors, gabapentinoids, oxybutynin, and clonidine. KM
    - Gabapentin is effective with drowsiness as a major side-effect compared to SSRIs/SNRIs. ⊕⊕⊕◯ B
    - Oxybutynin, approved to treat overactive bladder, has shown effectiveness in reducing VMS. ⊕⊕⊕◯ B
    - Paroxetine should be avoided in women receiving tamoxifen due to its effect on CYP2D6. ⊕⊕⊕◯ B
    - Stellate ganglion blockade has been shown to be effective in small trials, but skilled operators are required to perform it. ⊕⊕⊕◯ B
    - Clonidine is no longer recommended as a first-line treatment due to low potency and side effects. ⊕⊕◯◯ C
- The duration of treatment of VMS with non-hormonal agents should be reviewed periodically, as with hormonal interventions. GPP

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5. Genitourinary Syndrome of Menopause and Sexuality

Genitourinary syndrome of menopause (GSM) is a multifaceted condition comprising different components such as vulvovaginal atrophy (VVA), bladder and pelvic floor dysfunction, and sexual function changes, which can have a significant impact on quality of life and intimate relationships [1]. A constellation of self-reported symptoms may be variably present, of which vaginal dryness and dyspareunia are the commonest. The reported prevalence ranges from 14% to 87% in postmenopausal women and depends on a whole variety of factors [2]. Bladder and pelvic floor conditions also increase at midlife and so does hypoactive sexual desire disorder (HSDD), which may co-exist with GSM along with other sexual function changes including arousal and orgasmic dysfunction. The decline in estrogen levels and intrinsic aging-related changes are the main factors associated with the manifestation of GSM symptoms [3], and the concomitant decline in androgen levels may also be a contributor influencing both genitourinary and sexual health. Other intrapersonal and interpersonal factors may be involved, influencing sexual self-image and relationship.

A multidimensional approach is the cornerstone of adequate diagnostic and therapeutic management of GSM. Many barriers to addressing GSM still exist and education with a culturally sensitive approach is mandatory [4]. The diagnosis of GSM is based on patient-reported symptoms in validated scales. Physical signs collected on clinical examination are confirmatory and allow the exclusion of other conditions that may co-exist or mimic GSM symptoms [5]. Laboratory investigations are not usually required. Treatment should be focused on the most distressing symptoms [6] and standardised outcomes should be assessed [7]. Those with bladder and pelvic floor dysfunction, sexual function changes, and some specific conditions may benefit from more targeted care pathways.

Below is a narrative summary of the evidence-based guidance for the management of GSM and sexual quality of life in menopausal women.

Treatment Options

The main principles of treatment in women with established GSM are the restoration of genitourinary functional anatomy and the alleviation of symptoms [8,9]. In a systematic review, the use of GSM-specific treatments ranged from 13% to 78% with over-the-counter lubricants and moisturizers being the most popular, followed by low dose vaginal estrogen therapy [10]. Systemic MHT was also used to some extent.

Non-hormonal pharmacological therapies

Vaginal and topical lubricants and moisturizers are considered first-line treatments of GSM [4,8,9,11]. Lubricants, which can be water, silicone or oil-based, are used during sexual activity to provide short-term relief. Moisturizers can be used daily or several times per week and provide longer lasting effects as they rehydrate the vaginal tissues and mimic vaginal secretions. The chemical composition of lubricants and moisturizers can vary significantly in pH, osmolality and additives [12]. Products with an osmolality under 380 mOsm/kg are recommended to minimize the risk of epithelial damage. Hyaluronic Acid (HA) based vaginal moisturizers may provide some additional benefit in relieving dyspareunia but overall the current level of evidence is low [13].

Hormone therapies

Vaginal estrogen therapy, intravaginal DHEA (prasterone) and the oral selective estrogen receptor modulator (SERM) ospemifene are the main treatment options for GSM [14,15]. When GSM is not the only concern, MHT may also be used alone or in combination with other topical products [9].

Many different vaginal estrogen therapy formulations (tablets, rings, capsules, pessaries, creams, gels and ovules) are available in different communities, with a variety of different estrogen molecules (estradiol (E2), estriol (E3), promestriene, conjugated equine estrogens (CEE) and estrone (E1)) [14].

Treatment should be started with daily application for the first 2-3 weeks followed by a maintenance application 1 to 3 times/weekly (with the exception of the ring which lasts 3 months). The estradiol (E2) dosage is low, 4 to 10 µg/day, which minimizes systemic absorption and ensures that circulating E2 levels remain below the mean for healthy, untreated postmenopausal women (<10.7 pg/ml). Used at the manufacturer-recommended dosages, low dose vaginal estrogen therapy does not require progestogen addition to protect the endometrium [9,16]. Higher doses of vaginal creams such as E2 (0.1 mg/g) and E1 (1 mg/g) are not considered safe for long-term use and higher doses may require the addition of a progestin for endometrial safety. 0.625 mg CEE vaginal cream may be used in the short-term e.g. 3-6 months and 0.3mg CEE is safe up to 1 year [9].

In the most recent Cochrane systematic review, vaginal estrogen therapy was superior to placebo in improving the symptoms of VVA, however, with low-quality evidence [17] and there was no difference in efficacy or adverse effects between the various available vaginal estrogen therapy preparations. Other systematic reviews support these findings and found that vaginal estrogen therapy was superior to vaginal lubricants and moisturizers on objective, but not subjective, clinical endpoints of VVA [18]. The 2021 EMAS Guidelines concluded the long-term safety of vaginal estrogen therapy [19] and a worldwide meta-analysis of epidemiological studies concluded that vaginal estrogen therapy was not associated with excess breast cancer risks [20].

The initial benefits of vaginal estrogen therapy may be observed within the first few weeks of treatment and are more evident by 12-16 weeks if compliance is maintained. Continuation of treatment is recommended as the signs and symptoms of GSM may reappear within a few weeks after stopping vaginal estrogen therapy [21]. Vaginal estrogen therapy may be less effective in women with established severe GSM or in those over 60 years of age [22], so the early introduction of such treatment may prevent more severe and intractable symptoms at a later date. Vaginal estrogen therapy can be continued indefinitely at the lowest effective dose for as long as benefit is noted and no significant risk emerges [23].

DHEA (prasterone) is a vaginally delivered steroid with intracrine estrogenic and androgenic activity that does not significantly increase circulating sex steroid metabolites [24]. After 12 weeks, it significantly reduced moderate-severe GSM symptoms and sexual pain in postmenopausal women and also had a positive effect on other domains of sexual function and objective outcomes [24,25]. Endometrial safety was confirmed for at least 52 weeks [26].

Ospemifene is an oral SERM which is effective in treating vaginal dryness, dyspareunia and other VVA symptoms at a daily dose of 60 mg [27]. In a network meta-analysis, ospemifene was not statistically

different from other active therapies (vaginal estrogen therapy, DHEA) in most efficacy and safety parameters, including endometrial thickness, with up to 52 weeks of treatment [28].

Laser and other thermal energy devices

Whilst laser (micro ablative fractional CO2 and non-ablative erbium lasers) and other thermal energy devices (different generations of radiofrequency) have gained recent popularity, there is still a limited body of supportive evidence [29]. Any side effects are mild and transitory [30] but long-term safety has not been established and NICE currently recommends that vaginal laser therapy should only be used in the context of research [31].

Urinary symptoms

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 [32]. Although a substantial body of epidemiological literature suggests an association between menopause and urinary tract symptoms, recurrent urinary tract infections (rUTIs) and other pelvic floor disorders [33], other factors than menopause, including the concurrent effects of aging and other comorbid conditions, may be contributory, and a causative link between the menopause and the pathogenesis of urinary tract symptoms has not been clearly established [34].

There is a consistent and clear difference between the effects of systemic MHT and vaginal estrogens on urinary symptoms in postmenopausal women [34,35]. Systemic MHT appears to be no more effective than placebo, and in some studies either worsened existing incontinence or was associated with the development of de novo incontinence. By contrast, vaginal estrogen therapy improves a range of urinary symptoms such as urinary frequency, urgency and stress urinary incontinence (UI), and is also effective in the prevention of rUTIs [34,35]. Vaginal estrogen therapy is recommended to reduce the risk of future UTIs in women with rUTIs and as an option for the treatment of overactive bladder (OAB) [11]. Whilst some initial studies have suggested a possible beneficial effect for non-estrogen-based interventions, such as DHEA, oral ospemifene and vaginal laser therapy, there are currently insufficient data to recommend these.

Changes in sexual function

The cluster of sexual symptoms which are an integral part of GSM includes dyspareunia, traditionally associated with VVA, and the various interconnected domains of the sexual response in postmenopausal women [1]. Hypoactive sexual desire disorder (HSDD), which encompasses low sexual desire and distress, is common and often coexists with GSM [36]. Both the 2018 IMS White Paper [37] and the 2024 EMAS clinical guide [38] highlighted the importance of sexual health and well-being for quality of life and intimate relationships. Given that both estrogens and androgens modulate the neural, muscular, and vascular systems contributing to a healthy sexual response, MHT may have a positive impact on sexual quality of life [39]. Estrogen alone leads to a slight improvement in sexual function compared to placebo [40] and vaginal estrogen therapy has a class effect on dyspareunia over placebo and may ameliorate the overall sexual response [41]. Transdermal testosterone therapy at a physiological dose is recommended in postmenopausal women with HSDD [42]. Psychoactive agents targeting the regulation of the complex neuroendocrine systems governing sexual excitation and inhibition have been studied in RCTs conducted in premenopausal women with HSDD [43]. Very recently, flibanserin, a centrally acting serotonergic modulator that functions as an agonist at 5-HT1A receptors and as an antagonist at 5-HT2A receptors, has been approved in naturally menopausal women with

HSDD based on the results of the 2014 SNOWDROP trial demonstrating clinically meaningful results of a daily oral 100 mg dose on frequency of satisfying sexual events, sexual desire, overall sexual function, and sexually related distress [44]. Psychosocial therapies, which include psychosexual therapy, CBT and mindfulness-based therapies, are an important approach in the treatment of HSDD and other changes in sexual function [45]. Additional therapies that may be of benefit include couples therapy [46] and pelvic floor muscle training (PFMT) [47].

Special populations

Some specific conditions require special consideration. Iatrogenic POI seems to be associated with a significantly higher rate of GSM and HSDD [48] and should be proactively treated with vaginal estrogen therapy [49]. Long-term sexual function changes are common after cancer treatment and only a minority get appropriate help, so specific enquiry is important [50]. GSM is more frequent and severe in breast cancer patients, especially those at a younger age and this can be exacerbated by adjuvant therapies that seek to create a hypoestrogenic environment. Non-hormonal lubricants and moisturizers should be considered first-line treatment and vaginal estrogen therapy should not be considered a first line treatment in those using an adjuvant hormone therapy [51]. However, vaginal estrogen therapy may be considered in individuals on tamoxifen or who do not require anti-estrogenic treatment. The limited data that are available on the safety of vaginal estrogen therapy after breast cancer supports its overall safety [52]. Shared decision-making on the individual benefits and risks of vaginal estrogen therapy and discussion with the oncologist are recommended before commencing hormone therapies [51]. Ospemifene, which acts as an anti-estrogen in breast tissue, is currently licensed for use in breast cancer survivors in Europe but not in the United States [53]. MHT is not generally recommended in women with a history of breast cancer.

In the majority of cases following gynecological cancer, systemic MHT can be used safely. However, in individuals who have had hormone-sensitive cancers, caution is advised and MHT may be contraindicated [54,55], although vaginal estrogen therapy may be acceptable [56].

Recommendations and Key Messages

Genitourinary Syndrome of Menopause (GSM)

- HCPs should be aware that vulvovaginal atrophy (VVA) and genitourinary syndrome of menopause (GSM) are not identical. GSM includes a wider range of signs and symptoms that may have different causes. GPP
- HCPs should be aware that GSM is very common, clinical presentation may be variable and GSM may have a big impact on quality of life. ⊕⊕⊕⊕ A
- HCPs should be proactive in screening and diagnosing GSM because the impact of the condition is underestimated and inadequately treated. ⊕⊕◯◯ C
- HCPs should offer individualized treatment considering evidence-based data, preferences and needs of women, and access to different options. GPP
- HCPs should treat symptomatic GSM with the aim of improving quality of life and intimate relationships. ⊕⊕⊕⊕ A
- HCPs should be aware and inform women that GSM is a chronic condition that does not resolve without treatment and may return upon discontinuation of therapy. ⊕⊕⊕◯ B
- Long-term treatment is often required as symptoms can recur on cessation of therapy. ⊕⊕◯◯ C
- Systemic risks have not been identified with vaginal low-potency/low-dose estrogens. ⊕⊕⊕◯ B
- HCPs should consider treating asymptomatic women with signs of GSM because symptoms may develop over time and women may benefit from early treatment. GPP
- HCPs should offer vaginal estrogen therapy to improve genitourinary and sexual symptoms associated with the menopause. ⊕⊕⊕⊕ A
- HCPs should consider adding vaginal estrogen therapy if GSM symptoms persist when using MHT. ⊕⊕◯◯ C
- HCPs should be aware that intravaginal DHEA and ospemifene are alternative options to vaginal estrogen therapy. ⊕⊕⊕◯ B
- HCPs should be aware that there is a lack of data comparing the effectiveness of vaginal estrogen therapy, DHEA and ospemifene for vaginal dryness and dyspareunia. ⊕⊕◯◯ C
- HCPs should offer treatment with vaginal lubricants and moisturizers to women with symptoms of vaginal dryness and dyspareunia. Vaginal lubricants and moisturizers can be used alone or combined with other treatments. ⊕⊕⊕⊕ A
- HCPs should be aware that there is a lack of data regarding the use of systemic or vaginal testosterone for the treatment of GSM. GPP

- HCPs should review women with GSM annually or when it is clinically needed. GPP
- HCPs can consider offering different products with long-term use because response to treatment or availability of products may vary. GPP
- HCPs should be aware that long-term safety varies among different treatments depending on their characteristics. ⊕⊕⊕◯ B
- HCPs should inform women that there is insufficient evidence to recommend the use of laser therapy. ⊕⊕◯◯ C
- HCPs should inform women that there is insufficient evidence to recommend the use of complementary medicines/therapies. GPP
- HCPs should consider referring women to a physiotherapist when pelvic floor abnormalities are associated with GSM. ⊕⊕◯◯ C
- HCPs should consider referring women to a psychotherapist/sex therapist when psychosexual factors are associated with GSM. ⊕⊕◯◯ C

Bladder and pelvic floor

- There is a wide variation in symptoms and signs of urogenital aging. ⊕⊕⊕⊕ A
- HCPs should be aware that lower urinary tract symptoms such as urinary frequency, nocturia and urgency are extremely common in postmenopausal women and the prevalence of incontinence in women increases with age. ⊕⊕⊕⊕ A
- HCPs should be aware that the co-existence of bladder symptoms and the menopause does not necessarily mean that menopause is the prime causative factor. ⊕⊕⊕◯ B
- Lifestyle changes and bladder retraining are recommended as first-line therapy for overactive bladder symptoms. ⊕⊕⊕⊕ A
- All women complaining of stress urinary incontinence will benefit from pelvic floor muscle training in the first instance. ⊕⊕⊕◯ B
- Vaginal estrogen therapy should be considered in postmenopausal women with lower urinary tract symptoms. ⊕⊕⊕⊕ A
- Vaginal estrogen therapy is recommended for the prevention of recurrent urinary tract infections (RUTIs). ⊕⊕⊕⊕ A
- HCPs should be aware that the optimal preparation and duration of vaginal estrogen therapy is not known. GPP
- Antimuscarinic drugs, combined with vaginal estrogen therapy, constitute first-line medical treatment in postmenopausal women with symptoms suggestive of an overactive bladder. ⊕⊕⊕⊕ A

- The use of systemic MHT does not seem to prevent urinary incontinence and is not recommended in the management of urinary incontinence or recurrent lower urinary tract infections. ⊕⊕◯◯ C

- There is currently insufficient evidence to recommend non-estrogen based therapies such as DHEA, ospemifene and vaginal laser for the management of urinary symptoms in postmenopausal women. ⊕◯◯◯ D

Sexual Function

- HCPs should be aware that menopause can have a significant impact on sexual well-being and function. ⊕⊕⊕⊕ A

- HCPs should introduce the topic of sexuality routinely and sensitively during menopause consultation. GPP

- HCPs should follow a standard process of care for assessment and management of the most common changes in sexual function, that is, hypoactive sexual disorder (HSDD). GPP

- HCPs should recognize and effectively treat GSM as part of the management of changes in sexual function even though there is insufficient evidence of improvement in overall sexual function. GPP

- HCPs should be aware that personalized management using the biopsychosocial model is needed to improve the quality of sexual life. GPP

- HCPs should consider the general and sexual health of the partner, as well as intimacy and relationship issues, to address sexual symptoms in partnered women. GPP

- HCPs should be aware that MHT prescribed for other indications may improve sexual function, although the benefit is generally small. ⊕⊕⊕⊕ A

- HCPs should consider the use of transdermal testosterone, in doses that approximate physiological premenopausal testosterone, to treat changes in sexual function in menopausal women with a diagnosis of HSDD. ⊕⊕⊕⊕ A

- HCPs should be aware that evidence to use other pharmacological strategies e.g, bremelanotide to treat menopausal sexual symptoms is limited. Very recently, flibanserin has been FDA approved for use in menopausal women. GPP

- HCPs should counsel on the insufficient evidence of complementary medicines/therapies in enhancing specific domains (desire, arousal, orgasm) of the sexual response. ⊕◯◯◯ D

- HCPs should be aware that the use of psycho-education is proven to have valuable benefits in postmenopausal women. ⊕⊕◯◯ B

- HCPs should consider individual and interpersonal psychosocial interventions to improve menopausal changes in sexual function. ⊕⊕◯◯ B

Special populations

POI

- HCPs should offer vaginal estrogen therapy to improve genitourinary and sexual symptoms. ⊕⊕⊕⊕ A
- Women with POI may be offered vaginal estrogen therapy if genitourinary symptoms are not fully relieved by using systemic HT. ⊕⊕⊕◯ B
- Vaginal lubricants and moisturizers can be used for the treatment of vaginal discomfort and dyspareunia in women with POI and can be combined with other treatments. ⊕⊕⊕⊕ A
- There is currently insufficient evidence to recommend vaginal laser or thermal energy for the management of genitourinary symptoms in women with POI. GPP

Breast cancer and other gynecological cancers

- HCPs should be aware that GSM is frequent and can be severe in breast cancer survivors. ⊕⊕⊕◯ B
- HCPs should offer vaginal lubricants and moisturizers for treatment of vaginal dryness and dyspareunia in women with GSM as first-line treatment. ⊕⊕⊕⊕ A
- HCPs should be aware that when limited evidence is present, the most conservative strategy to treat GSM should be applied. GPP
- Vaginal estrogen therapy, DHEA or ospemifene should not be used as the first line in breast cancer survivors. GPP
- HCPs may consider vaginal estrogen therapy, DHEA or ospemifene in individual breast cancer survivors taking into account evidence-based data, tumour characteristics, the preferences and needs of women, and access to different treatment options. GPP
- HCPs should be aware that for the majority of gynecological cancers, vaginal estrogen therapy, prasterone or ospemifene can be used but attention should be paid to the tumour characteristics. ⊕⊕◯◯ C
- HCPs should inform women that there is currently insufficient evidence to recommend vaginal laser or thermal energy for the management of GSM. ⊕⊕◯◯C

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6. Osteoporosis

Introduction

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). Osteoporosis and associated fractures is the most common chronic metabolic bone disease and represents a major global health problem contributing to 8.9 million fractures worldwide on an annual basis [1]. About 1 out of every 3 postmenopausal women will experience an osteoporosis related fracture in their lifetime, but there are marked variations worldwide in the rates of hip fracture and major osteoporotic fractures [2]. Fractures associated with osteoporosis cause not only increased morbidity but also an increased mortality [3].

Bone strength is determined by a combination of bone mineral density (BMD) and microarchitectural integrity. Postmenopausal osteoporosis may result from a failure to attain peak bone density, accelerated bone loss after menopause, age-related bone loss, the effect of secondary disease conditions and medications or a combination of several factors.

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. Hip fracture is responsible for the largest proportion of the financial burden of osteoporosis to healthcare systems but other osteoporosis-related fractures, particularly vertebral fractures, cause considerable morbidity. The truth is that osteoporosis is underdiagnosed and undertreated [4].

The role of the menopause

Accelerated postmenopausal bone loss in women is induced by ovarian derived estrogen deficiency. Lack of estrogen induces upregulation of the Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) and a decreased expression of osteoprotegerin. This stimulates osteoclastic recruitment and function, resulting in increased bone resorption, with lowering of BMD, deterioration of microarchitecture and decreased bone strength [5]. The close relationship between menopause and deleterious bone effects has been examined in depth in the Study of Women's Health Across the Nation (SWAN). This is a longitudinal study of 3302 women followed from perimenopause for more than 20 years with a subset of 2407 participants that had serial BMD estimations [6]. Bone loss occurs from 1-2 years before final menstrual period till 3-4 years after final menstrual period, at both the lumbar spine and femur neck. Bone loss is maximal in the period one year before FMP and continues for 2 years after the final menstrual period with cumulative BMD loss averages during this time of 10.6% at lumbar spine and 9.1% at the femur neck [7]. Trabecular Bone Score (TBS), an independent indicator of bone strength, declines by 1.16% annually from 1.5 years before the FMP with a loss of 6.3% over the menopausal transition. This is very important as micro-architectural damage to the trabecular structure cannot be corrected with anti-resorptive therapy [8]. BMD at the time of menopause is a highly significant predictor of the risk of future osteoporosis as significant bone loss (and loss of bone structure) will lead to earlier attainment of fracture thresholds [9].

These findings strengthen the understanding of the difference between preventing osteoporosis (bone loss) and prevention of fractures. Prevention of osteoporosis is generally applicable to the younger women (peri and early menopause) whilst prevention of fracture is generally applicable to older

women presenting with low BMD and other risk factors for fracture. The peri- and early menopause are a golden opportunity to prevent osteoporosis and bone loss, with a variety of medications and MHT being the most obvious choice.

Diagnosis and assessment

The diagnosis of osteoporosis is based on assessment of BMD by Dual X-ray Absorptiometry (DXA) or the presence of a fragility fracture.

The role of BMD

BMD estimations became a reality with the advent of Dual Energy X-ray Absorptiometry (DXA) Scanners in the late 1980s and central DXA-derived BMD values remain the gold standard. A World Health Organization (WHO) study group, in 1994, defined osteoporosis as a BMD of 2.5 or more standard deviations below the mean value of young healthy white women (T-score). The setting of a T-score threshold of $\leq$-2.5 was an epidemiological classification. However, randomized controlled studies to prove anti fracture efficacy of new drugs used a T-score of $\leq$-2.5 as an inclusion criterium [10]. As efficacy was proven in those patients, it was widely accepted as an intervention threshold and still remains embedded in most guidelines. It is important to understand that BMD is only one of the risk factors for fracture. Indeed, the majority of fractures occur in women with osteopenia (low BMD) with a BMD T-score between -1.0 and -2.5 [11]. This is indicative of high specificity but low sensitivity of using T-score as a single risk factor for fracture. It is thus important to consider the significance of low BMD in the presence of other risk factors for fracture such as advanced age, a personal or family history of fractures, a history of early menopause or POI, low BMI, inadequate diet, smoking, alcohol abuse, the use of bone-toxic medications, diabetes and rheumatoid arthritis. The need for treatment can be better defined by fracture risk probability over time. Many models have been designed to integrate these risk factors into a predictive fracture risk calculation over a period of time, one of which is the FRAX model (https://www.fraxplus.org/calculation-tool/) [12]. It is based on fractures recorded in large cohorts including the placebo arms of many modern randomized controlled trials (RCTs) used to establish the efficacy of new bone-specific drugs. It is an internet-based tool that calculates the 10-year probability of hip fracture or a major osteoporotic fracture (MOF). FRAX has been externally validated in independent cohorts and calibrated to the epidemiology of fracture and death in different countries. FRAX can be used without DXA. Software applications added to DXA now also allow calculation of trabecular bone score (TBS) that is an additional reflection of bone strength. If available, it is recommended that the FRAX prediction be adjusted by TBS. It is recognized that FRAX has shortcomings such as not incorporating spine BMD, risk of falls, type 2 diabetes, quantification of glucocorticoid treatment, recency of fractures and Parkinson's disease. Some arithmetic adjustments have been proposed as compensation [13]. The value of FRAX in the peri/early menopause has been questioned. FRAX predictions are country specific and calculated using country specific hip fracture incidence and mortality figures.

The role of fractures

Fragility fractures result from mechanical forces that would not ordinarily result in a fracture [12]. The WHO has further quantified this as forces equivalent to a fall from a standing height or less. Fragility fractures of the spine, hip, forearm, humerus or pelvis are generally accepted as being signs/ manifestation of osteoporosis and an indication for treatment.

The risk of a subsequent osteoporotic fracture is highest immediately after the first (index) fracture and decreases progressively with time [14]. This risk is especially high in the first 2 years post index fracture [15].

The risk of a subsequent fracture is also increased in the presence of multiple fractures.

In the case of asymptomatic morphometric fractures of the spine, the grade of the fracture (mild, moderate or severe) most likely also correlates with risk of subsequent fracture [16]. This can be determined by vertebral fracture assessment (VFA), a function of most modern DXA-devices, or by conventional X-rays. VFA adds valuable information to the interpretation of any DXA study.

Based on fracture history, the American Association of Clinical Endocrinologists/ American College of Endocrinology guidelines stratify patients at very high risk of fracture as those with a recent fracture (within the past 12 months), those that have fractures while on approved osteoporosis therapy, multiple fractures or fractures while on drugs causing skeletal harm (such as long-term glucocorticoid therapy) [17]. The US Endocrine Society adds a severe fracture to this list [18].

Intervention thresholds

It is important to understand that FRAX only predicts future risk of fracture and as such does not provide information of when to treat it. Intervention thresholds can be calculated in 2 different ways: a country specific age adjusted intervention threshold is set at a risk equivalent to that associated with a prior fracture in a woman of the same age with average BMI. The best example of such a model is the one developed by the National Osteoporosis Guideline Group of the UK (NOGG) [13]. It is a hybrid model that compensates for possible inequalities in treatment with younger individuals likely to be overtreated and older individuals with no fracture history to be undertreated. An age-dependent intervention threshold is used up to the age of 70 and a fixed threshold is adopted thereafter [19]. Intervention threshold tables are available for risk of MOF or hip fracture. Age dependant fracture risk is stratified as low, high or very high. If FRAX was used without hip BMD, the need for DXA is negated.

An alternative is to use fixed values such as USA intervention threshold which defines a risk of MOF exceeding 20% or hip fracture risk exceeding 3% over 10 years, without regard to age. This model is based on 2005 USA economic factors but is still in use in many countries [20]. These fixed values have been blindly copied by many countries without taking into account local epidemiology of fractures or health economics.

Stratification of risk

Classifying the stratification of fracture risk as low, high or very high is important to individualize therapy [21]. This is easy using a country specific age adjusted intervention threshold such as suggested by NOGG, but becomes more complicated when such threshold is not available. The details related to the risk stratification are presented in a hybrid model of various guidelines as published in the IMS White Paper [22] (Table 1).

Screening for osteoporosis

The US Preventative Task Force, in their 2025 recommendation statement, suggests that screening for osteoporosis and risk of fractures must entail a DXA examination. They recommend that all women ≥ 65 years should be screened, if not screened before. Women younger than 65 years should be screened when indicated in clinical risk assessment [23]. This is problematic as FRAX has been shown

to underestimate risk in younger women. It is suggested that the Osteoporosis Self-Assessment Tool (OST) based on age and weight alone (when score <2), or the Osteoporosis Risk Assessment Instrument (ORAI) when score <9, are better in predicting low BMD [24].

NOGG 2024 recommends that FRAX without DXA should first be done to determine the need for DXA using the country specific intervention model.

Further work needs to be done to identify women at risk of excessive bone loss at peri/early postmenopause.

Strategies for the prevention of fractures

Lifestyle changes

Given the known accelerated bone loss that occurs with menopause, all postmenopausal women should be educated on a bone-friendly lifestyle. This includes optimization of calcium and vitamin D status/level, appropriate exercise, cessation of tobacco smoking and excessive alcohol intake and the minimisation of bone toxic medications (such a glucocorticoids, protein pump inhibitors, aromatase inhibitors).

Calcium, vitamin D and other dietary measures

Postmenopausal women need a dietary reference intake (DRI) of 1000–1500mg of elemental calcium. Sufficient intake is based on diet history, and serum calcium levels do not assist with this. Calcium supplementation should be restricted to bridge the shortfall between dietary intake and the DRI. 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. Calcium supplementation alone may provide a small improvement in BMD [25]; however, it has not been proven efficient at reducing fractures in postmenopausal women with low BMD [26].

The DRI for vitamin D is 400-600 IU per day in the postmenopausal period, although 800 to 1000 IU per day is recommended by the International Osteoporosis Foundation for those over 60 years and alternatively by the Bone Health and Osteoporosis Foundation for those over 50 years [27,28]. As the major source of vitamin D is sunlight exposure, the need for supplementation will vary, and will be based on location, time spent outdoors, skin exposure and skin tone. Measuring the blood 25-hydroxyvitamin D level may be helpful in selected cases, although there is controversy regarding the optimal Vitamin D level for post-menopausal women. A level of <50nmol/L is generally considered insufficient, and levels >125nmol/L may be considered potentially harmful [29]. Supplementation is generally recommended to those with Vitamin D insufficiency, to increase levels to the optimal range. In a recent meta-analysis of vitamin D supplementation in adults, vitamin D has been shown to independently reduce the risk of falling in elderly / institutionalised women [30]. In postmenopausal women with low BMD, the meta-analysis suggests that Vitamin D alone may reduce non-vertebral fractures but has no effect on vertebral or hip fractures. However, studies of vitamin D supplementation are limited by varied dosages and not stratifying results by baseline vitamin D status.

The combination of calcium and vitamin D supplementation may provide additional benefits. Meta-analyses of postmenopausal women with low BMD have demonstrated a reduced risk of hip fractures with combined calcium and vitamin D [31].

Vitamin K is needed for the carboxylation of osteocalcin to enable binding with calcium and phosphate and thereby facilitating bone mineralization. The RDI is 70-90 microg in the postmenopausal period. Studies have demonstrated inconsistent effects of Vitamin K supplementation on BMD, with possible small increase in lumbar spine BMD, but no effect at other sites [32,33,27]. Evidence for fracture reduction is inconsistent, and limited by the quality of trials, heterogeneity between trials and duration of follow up. Given this, routine supplementation (and testing of vitamin K levels), is not recommended for postmenopausal women.

There is no clear evidence for other dietary interventions or supplements. Protein supplements or increasing protein intake has inconsistent effects on BMD in RCTs, and there is no evidence for fracture reduction [34,35]. Observational studies, however, have linked higher protein intake to higher BMD, and given that inadequate protein intake can contribute to sarcopenia (see Section 7 Sarcopenia), in turn increasing falls risk, postmenopausal women should be encouraged to have adequate protein intake as per DRI [36]. Isoflavones, particularly genistein or ipriflavone, may improve BMD when taken for >12 months. However, the magnitude of change is small, and there is heterogeneity among studies [37,38,39]. Meta-analyses of probiotics and kidney tonifying Chinese medicines have suggested possible improvements in BMD; however, those studies were rather small, with significant heterogeneity and significant risk of bias [40-43].

Exercise

Global recommendations for exercise suggest that all adults should do at least 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic physical activity per week, as well as muscle-strengthening activities involving all major muscle groups on 2 or more days a week (WHO). Few studies have examined the effects of exercise on fracture prevention in postmenopausal women overall (as opposed to those with known osteoporosis). Many studies report fractures as an adverse effect of exercise rather than a primary outcome and are underpowered and /or of insufficient duration to assess this. A systematic review analysing any exercise interventions of at least 6 months duration in postmenopausal women reported less fractures in those allocated to exercise groups compared to control groups (19/387 versus 34/366) [44]. A 2011 Cochrane review concluded that exercise may slightly reduce fractures in post-menopausal women, but that this result may be due to chance [45].

The effects of exercise on bone health may depend on the type, intensity and frequency of exercise, and so the systematic reviews examining different combined exercise interventions find inconsistent results with high heterogeneity [46]. Multicomponent exercise programs, particularly involving dynamic resistance training and weight-bearing / aerobic exercises, have been shown to improve BMD at both the lumbar spine and hip level [47-50]. In addition, moderate intensity exercise may be the most effective option for increasing BMD [51,52].

Water based exercises, whole body vibration exercises and pilates have inconsistent effects on BMD, the magnitude of change is small, and study quality is variable [53-56]. The effects of Tai Chi and other traditional Chinese exercises may depend on the style / type of Tai Chi. When analyzed by style, certain exercises such as Baduanjin, Taiji and Yijinjin may improve BMD particularly at the lumbar spine although the magnitude of change in small [57,58]. Aside from effects on BMD, Tai Chi may also prevent falls - a leading cause of fractures [59].

Pre-treatment assessment

A detailed interview must be carried out to exclude treatable secondary cause of osteoporosis, previous fractures, to identify modifiable lifestyle changes and assess general medical condition and medication.

The extent of osteoporosis should be defined by VFA or conventional X-ray to screen for asymptomatic vertebral fractures and if present to grade the fracture(s) by the semi-quantitative method of Genant (mild, moderate or severe) [60].

Appropriate blood tests, as per national guidelines, should be done to exclude secondary (treatable) causes of bone loss. This may include serum levels of calcium, phosphate, Vitamin D, parathyroid hormone (PTH), serum protein electrophoresis, full blood count, glomerular filtration rate, gluten intolerance screens and 24-hour urinary estimation of calcium and phosphate excretion.

Bone Specific Pharmacological Interventions:

A. Anti-resorptive treatment

1. Menopausal Hormone Therapy (MHT)

As explained before, estrogen is nature's own anti-osteoporotic drug, acting mainly by downregulation of RANKL. The use of MHT in general has been limited by perceived fears regarding risks, especially breast cancer and thromboembolic events. This was largely based on misinterpretation of the initial WHI results. The benefit-risk ratio has been put into perspective by long term follow-up of the WHI cohort [61,62].

MHT decreases the incidence of all fractures, including vertebral, non-vertebral and hip fractures, even in women at low risk of fracture [63]. Meta-analysis reported 388 fewer fractures with estrogen-only therapy over 7.2 years and 230 fewer fractures with combined MHT over five years per 10,000 persons [64]. Although MHT prevents bone loss at any age after the menopause, the age of the initiation of MHT is important. If initiated in the age group 50–60 years or within 10 years after menopause (the window of opportunity), the benefits of MHT are most likely to outweigh any risk [65]. This makes MHT an ideal candidate for the prevention of menopause associated bone loss. Recent opinion based on re-evaluation of the WHI data advocates that the window of opportunity should be revisited as being too restrictive and denying many deserving women the benefit of MHT, especially in terms of bone health [66]. Initiation of MHT at the age group of 60–70 years requires an individually calculated benefit-risk ratio as well as consideration of other available medications. There are no large RCTs assessing the prevention of fracture in osteoporotic women but there is no reason to suspect that MHT would not be effective.

There is no mandatory time limit for duration of MHT, provided that it is consistent with the treatment goals [67]. 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. A recent systematic review included two small studies which indicated that sequential therapy with alendronate or raloxifene treatment for 12 months post MHT cessation increased or maintained spine and femoral neck BMD [68]. Continuation of MHT beyond the age of 65 for the sole purpose of the prevention of fractures should be consistent with the lowest effective dose, transdermal rather than oral route and estradiol (E2) rather than conjugated equine estrogen (CEE). In women who

continued MHT beyond age 65, compared to cessation at 65 or never users, many health advantages were shown, especially with estrogen monotherapy [69].

Evidence for the fracture-protective effect of MHT is limited to standard dosages of CEE and medroxyprogesterone acetate (MPA), administered by the oral route. Evidence for protection against loss of BMD is strong for lower than standard doses with oral and transdermal administration [70].

Tibolone, a synthetic preparation metabolized to molecules that have affinity to estrogen, progesterone and androgen receptors protects against vertebral and non-vertebral fractures in older women, as presented in an RCT and meta-analysis [71,26].

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 [72].

No significant effect of testosterone therapy on BMD in postmenopausal women was reported in a systematic review and meta-analysis of RCT data [73].

2. Bisphosphonates (BPs)

BPs are the most commonly prescribed therapy for the treatment of postmenopausal osteoporosis. BPs act by inhibiting farnesyl pyrophosphate synthase in the mevalonate pathway, thus inhibiting osteoclast function and survival. BPs bind to bone surface at different strengths and remain in bone for lengthy periods dependant on the strength of the binding. Intravenous (IV) zoledronate binds strongest to bone, followed by oral alendronate or oral risedronate (both administered weekly), and oral ibandronate (administered monthly) or risedronate (administered monthly). Because of the extended action in bone, BPs are ideal to follow after other anti-resorptive or anabolic drugs as cessation of these drugs is followed by rapid bone loss.

BPs are potent inhibitors of bone resorption with proven efficacy in the prevention of vertebral (50-70%), non-vertebral (20-30%) and hip fractures (40-50%) in large RCTs and meta-analyses [74]. A recent Cochrane review reported that alendronate is associated with a clinically important reduction in vertebral but not hip or wrist fractures as primary prevention, although a reduction in vertebral, hip and wrist fracture is observed as secondary prevention [75]. An updated Cochrane review of risedronate concluded no significant benefit for primary fracture prevention of osteoporotic fracture, but risedronate (5mg daily) significantly reduced non-vertebral and hip fractures with unclear effect on vertebral fracture [76]. Ibandronate has been shown to reduce the risk of hip fracture only in women at high risk of hip fracture [77]. Zoledronate is effective in reducing vertebral and non-vertebral fracture risk for both primary and secondary prevention [78]. When given shortly after hip fracture, the annual dose of zoledronate 5mg has been proven to reduce number of clinical fractures and mortality after 3 years in both men and women [79].

In postmenopausal women with osteopenia, meta-analyses indicate that bisphosphonate therapy reduces the risk of fragility and vertebral fracture for primary prevention [80]. A 2023 meta-analysis of perimenopausal or <five years postmenopausal women without osteoporosis (12 RCTs; n=1722) reported improved lumbar spine, femoral neck and hip BMD with oral or IV bisphosphonates versus placebo, although fracture outcomes were lacking [81]. A recent RCT, where zoledronate 5 mg IV was

administered at baseline and after 5 years, showed efficacy in preventing bone loss and morphometric vertebral fracture in early postmenopausal women of average BMD, after 10 years [82].

The frequency and types of adverse events vary with the type of bisphosphonate [83]. Common side-effects of oral BPs include upper gastrointestinal symptoms, bowel disturbance, headaches and musculoskeletal pain. Zoledronate infusion may cause an acute phase flu-like reaction which can be reduced by co-administration of paracetamol or dexamethasone. As BPs are solely excreted by the kidneys; glomerular filtration rate should be calculated to be >35ml/min prior to the initiation of treatment and recipients should be advised of a risk of kidney failure.

BP therapy may be associated with rare but serious adverse events, namely atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ). The optimal duration of bisphosphonate therapy thus becomes relevant as osteoporosis is a life-long disease.

Management should ensure that the benefit of fracture risk reduction at all times exceeds the small risk of AFFs and ONJ. When defining the optimal duration of treatment, the factors such as the persistent action of BPs after cessation, BMD increasing plateaus after 3-5 years and the small risk of AFF and ONJ, should be taken into consideration. Typical recommendations are a drug free period after 3 years of annual IV therapy and after 5 years of oral therapy. Exceptions are women at high risk of fracture, notably when older than 70, those with a previous fracture or those with fracture on treatment without change in treatment. In these patients treatment should persist for 6 years (IV) or 10 years (oral). Restarting treatment should be based on FRAX values determined after 18 months of risedronate and ibandronate, 2 years of alendronate, and 3 years of zoledronate [13]. After 10 years of BP treatment, patient management should be considered on an individual basis.

3. Denosumab

Denosumab was developed as targeted therapy and is a monoclonal antibody against RANKL, the regulator of osteoclast development and activity. Denosumab is given as a subcutaneous injection of 60 mg once every 6 months.

Denosumab has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis [84]. Safety and efficacy have been shown in 10 years of follow-up [85].

Denosumab differs from BPs in not being excreted via the kidneys and in the fact that the effect on BMD does not plateau after 3-5 years but increases during every year of treatment. Unlike BPs, denosumab cessation leads to rapid reductions in BMD and elevations in bone turnover to levels above those seen before treatment initiation, therefore an increased rate of multiple vertebral fracture [86]. Long-term treatment with denosumab can be considered for patients at high fracture risk in view of favorable efficacy and safety profile.

In case of denosumab discontinuation, alternative anti-resorptive treatment should be initiated 6 months after the final denosumab injection. A careful assessment of indications to start denosumab treatment is advised, especially for younger patients.

Hypocalcemia is a side-effect of denosumab treatment and should be excluded prior to treatment especially when renal impairment is present. Other side effects include cellulitis, eczema and rarely ONJ and AFF.

4. Selective Estrogen Receptor Modulators (SERMs)

SERMs have an estrogen-like effect on bone (although weaker) but oppose estrogen receptors (ER) in the breast and uterus. Raloxifene and bazedoxifene maintain BMD and reduce vertebral fractures in postmenopausal women with or without prevalent vertebral fractures [87]. Bazedoxifene prevents hip fracture in selected women at high risk of fracture [88]. Raloxifene reduces the risk ER+ breast cancer in osteoporotic women [89]. Raloxifene is indicated in asymptomatic women at risk of vertebral fracture and breast cancer. SERMs do not alleviate vasomotor symptoms associated with menopause. SERMs increase the risk of thromboembolic events.

B. Anabolic Agents

1. **Teriparatide** (recombinant human parathyroid hormone hPTH-(1-34)

Teriparatide, when administered intermittently as a daily subcutaneous injection of 20 ug, stimulates bone formation (anabolic effect) by activation of the osteoblast. The anabolic effect is most marked in trabecular bone. Duration of treatment is generally limited to 24 months as the anabolic effect weakens after that. Cessation of teriparatide leads to a rapid loss of BMD and should be followed by an anti-resorptive. Teriparatide has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis in an RCT [90] and meta-analyses [91], with greater fracture risk reduction versus risedronate or ibandronate [92]. Evidence for the reduction of hip fracture risk is based on systematic review and meta-analysis [93]. Prior treatment with a bisphosphonate may blunt the effect of subsequent teriparatide. PTH levels and serum calcium levels need to be normal prior to initiation of teriparatide. Side effects include headache, nausea, dizziness, postural hypotension and leg pain. Slight and transient elevations of serum calcium may occur following teriparatide injection. A recent systematic review concluded that there was no significant evidence of an increased risk of osteosarcoma with teriparatide [94]. Teriparatide biosimilars are now available.

2. Abaloparatide

Abaloparatide is a synthetic peptide analog of the first 34 amino acids of the human parathyroid hormone-related peptide (PTHrP). It has anabolic skeletal effects when given intermittently as a daily subcutaneous injection of 80 µg. The duration of treatment is limited to 18 months after which it should be followed by anti-resorptive therapy.

Abaloparatide increases lumbar spine, hip and femoral neck BMD. Abaloparatide has been shown in meta-analyses [95] to reduce vertebral fractures in postmenopausal women with osteoporosis. Other network meta-analyses [96] have demonstrated a reduction in non-vertebral fractures, with evidence suggesting that abaloparatide is more effective than teriparatide in lowering non-vertebral fracture risk. There are insufficient data to assess its efficacy against hip fracture.

Side effects include hypercalcaemia and hypercalciuria, dizziness, back pain, nausea, headache, arthralgia, hypertension, injection site reaction, and palpitations. Abaloparatide must not be used in people with severe renal impairment including patients with end-stage renal disease. Blood pressure, cardiac status and ECG should be assessed prior to beginning treatment with abaloparatide.

3. Romosozumab

Romosozumab was developed as targeted therapy and is a humanised monoclonal antibody that binds to and inhibits sclerostin. It has a dual action, stimulating bone formation and inhibiting bone resorption. It is given as a subcutaneous injection of 210 mg once per month for maximum duration

of 12 months after which it should be followed by anti-resorptive therapy. In a comparator-controlled study (ARCH) in postmenopausal women with severe osteoporosis, romosozumab 210 mg once monthly for 12 months and followed by oral alendronate 70 mg once weekly for 12 months was compared against alendronate 70 mg once weekly for 24 months. New vertebral, non-vertebral, clinical and hip fractures were all significantly lower in women treated with romosozumab followed by alendronate compared to treatment with alendronate alone [97]. Meta-analyses confirm these findings reporting decreased incidence of vertebral and non-vertebral fractures with romosozumab versus control at 24 months [98]. A significantly higher incidence of cardiovascular events was seen in the romosozumab group compared to the alendronate group. It is thus contraindicated if history of myocardial infarction or stroke is present. Network meta-analyses reported no increased risk of cardiovascular death or major events with romosozumab, although the certainty of evidence was low [99]. Hypocalcaemia should be corrected prior to initiation of treatment and patients should be adequately supplemented with calcium and vitamin D.

Anabolic treatment for women at very high risk of fracture

Two trials suggest that anabolic therapy should be considered as first line treatment in patients at very high risk of fracture. In the VERO study, postmenopausal women with severe osteoporosis received teriparatide or risedronate. After 24 months, teriparatide-treated women had a significantly reduced risk of vertebral and any clinical fracture with a non-significant trend in reduction of non-vertebral fractures compared to risedronate [100]. In the ARCH study as previously discussed, postmenopausal women with severe osteoporosis who first received 12 months of romosozumab followed by 12 months of alendronate had superior protection compared to the alendronate treated group after 24 months. A meta-analysis which included these studies, reported a 40% decreased risk of new vertebral fractures with anabolic agents compared to oral bisphosphonate therapy in women with osteoporosis at high or very high risk of fracture [101].

It should also be considered that prior BP therapy blunts the effect of following anabolic therapy.

Comparative efficacy of bone-specific drugs

It is difficult to show superiority of a certain drug because of few head-to-head studies. A recent systematic review and network meta-analysis found evidence that all the drugs as discussed (MHT not included in study) are effective in the prevention of clinical and vertebral fractures but bone anabolic treatments are more effective than bisphosphonates [102]. A different network meta-analysis included MHT and found that MHT and tibolone significantly reduce hip fractures, non-vertebral and vertebral fractures. Teriparatide, abaloparatide, denosumab, and romosozumab were associated with the highest relative risk reductions [26].

The summary of suggested treatments based on stratification of fracture risk is presented in Table 2.

Recommendations and Key Messages

- Women with osteoporosis should be advised that osteoporosis is a life-long disease and cannot be cured. Planning of the sequencing of drugs and possible drug-free periods should be addressed at the initiation of therapy. GPP
- The duration of therapy and the sequence of drugs and drug-free periods are drug-specific. KM
- Anabolic and anti-resorptive therapy should not be routinely combined. KM
- In sequential therapy, anabolic therapy should preferably be given before anti-resorptive drugs. ⊕⊕⊕⊕ A
- Postmenopausal osteoporosis and fractures are avoidable, serious conditions that are underdiagnosed and undertreated. ⊕⊕⊕⊕ B
- Menopause is associated with significant bone loss that is preventable with a variety of drugs. ⊕⊕⊕⊕ A
- Although osteoporosis is defined by low bone mineral density (BMD), this is only one risk factor for fracture. Estimates as to the probability of future fracture, as well as intervention thresholds, should take into account all risk factors. This can best be done using a risk calculator such as the Fracture Risk Assessment Tool (FRAX), Garvan or other population-specific risk calculators. ⊕⊕⊕⊕ A
  https://www.fraxplus.org/calculation-tool?country%E2%80%89=%E2%80%899
- Intervention thresholds should be based on FRAX probabilities for Major Osteoporotic Fractures (MOF) or hip fracture over the next 10 years. A country-specific age-adjusted intervention threshold should be calculated as a risk equivalent to that associated with a prior fracture in a woman of the same age with average BMI. The best example of such a model is that developed by the National Osteoporosis Guidelines Group (NOGG) UK. If not available, set threshold values should be used (USA model). GPP
- Stratification of the risk of fracture into low, high or very high is helpful in decision-making for the need and type of therapy. GPP
- All perimenopausal and early menopausal women should be screened by FRAX (without Dual-Energy X-Ray Absorptiometry [DXA]) or locally developed screening tools and with DXA if risk is established. All women should be screened by DXA at age 65 years if not screened before. GPP
- All postmenopausal women should be educated on a bone-friendly lifestyle, including physical activity (resistance/weight-bearing exercise and falls prevention) and diet containing the recommended calcium intake and Vitamin D. This is also an essential adjuvant to any pharmacological intervention. ⊕⊕⊕⊕ A

- MHT is first-line therapy for the prevention of menopause-related bone loss. Benefits are most likely to outweigh any risks when initiated within 10 years after menopause or before age 60 years. Cessation of therapy leads to rapid bone loss. MHT significantly reduces the risk of osteoporosis-related fractures. ⊕⊕⊕◯ A

- Bisphosphonates (BPs) are potent inhibitors of bone resorption with proven efficacy in the prevention of all osteoporosis-related fractures. It is indicated in women at high and very high risk of fracture. A drug-free period should be considered after 3 years of IV therapy and after 5 years of oral therapy. Restarting treatment should be based on FRAX values or markers of bone turnover (MBT) as determined after 18 months off risedronate and ibandronate, 2 years off alendronate and 3 years off zoledronate. Osteonecrosis of the jaw and atypical femoral fracture are rare complications. ⊕⊕⊕⊕ A

- The selective estrogen receptor modulator (SERM) raloxifene is indicated in asymptomatic women at risk of vertebral fracture and/or breast cancer. Additionally, bazedoxifene is also protective of hip fracture in women at high risk of hip fracture. ⊕⊕⊕◯ B

- Denosumab reduces the incidence of all osteoporosis-related fractures and is indicated in women at high and very high risk of fracture. There is no limit on the duration of therapy, but cessation is followed by accelerated bone loss and increased risk of fracture that mandates the use of an anti-resorptive drug, such as a BP. ⊕⊕⊕⊕ A

- Teriparatide is a bone anabolic agent that reduces the risk of all osteoporosis-related fractures. It is first-line therapy for women at very high risk of fracture. Duration of therapy is limited to 2 years, after which it should be followed by an anti-resorptive drug such as a BP or denosumab. ⊕⊕⊕⊕ A

- Abaloparatide is a bone anabolic agent that reduces the risk of vertebral and non-vertebral fractures. It is first-line therapy in women at very high risk of fracture. The duration of treatment is limited to 18 months, after which it should be followed by anti-resorptive therapy such as a BP or denosumab. ⊕⊕⊕◯ B

- Romosozumab has a dual action, stimulating bone formation and inhibiting bone resorption. It reduces all osteoporosis-related fractures, and is first-line therapy in women at very high risk of fracture. The duration of treatment is limited to 12 months, after which it should be followed by anti-resorptive therapy such as a BP or denosumab. ⊕⊕⊕⊕ A

- In women at very high risk of fracture, teriparatide, abaloparatide or romosozumab should precede anti-resorptive therapy. ⊕⊕⊕⊕ A

Table 1. Fracture risk stratification

RISK CATEGORY	CRITERIA
Low Risk (all must be present)	• No fragility fracture • DXA-derived T-score between **–1 and –2.5** (i.e., < –1 and > –2.5) • FRAX 10-year probability of fracture (TBS-adjusted): – Major osteoporotic fracture **< 20%** – Hip fracture **< 3%** – OR below the country-specific threshold for intervention
High Risk (any one of the following)	• Presence of a fragility fracture • DXA-derived T-score **< –2.5** • FRAX 10-year probability of fracture (TBS-adjusted): – Major osteoporotic fracture **> 20%** – Hip fracture **> 3%** – OR exceeding the country-specific threshold for intervention
Very High Risk (any one of the following)	• Recent fracture • Multiple fractures • Severe fracture • Fracture while on treatment • Fracture while on bone-toxic drugs (e.g., corticosteroids) • T-score **< –3.0** • FRAX 10-year probability of fracture (TBS-adjusted): – Major osteoporotic fracture **> 30%** – Hip fracture **> 4.5%** – OR exceeding the country-specific upper threshold for high risk • Other factors such as extremely high fall risk

Table 2. Fracture risk stratification – treatment recommendations

FRACTURE RISK LEVEL	TREATMENT RECOMMENDATIONS
Low Risk	• Optimize calcium and vitamin D status • Bone-friendly lifestyle
High Risk	• Optimize calcium and vitamin D status • Bone-friendly lifestyle • Falls prevention • Start appropriate anti-resorptive therapy
Very High Risk	• Optimize calcium and vitamin D status • Bone-friendly lifestyle • Falls prevention • Consider appropriate anabolic treatment followed by anti-resorptive therapy

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7. Sarcopenia

Introduction

Sarcopenia is a muscle disorder characterized by impaired strength, quantity, quality, and/or physical performance, leading to adverse outcomes such as disability, falls, and mortality [1]. While definitions vary, diagnostic frameworks from the European Working Group on Sarcopenia in Older People (EWGSOP2), the Asian Working Group for Sarcopenia (AWGS), and the Sarcopenia Definitions and Outcomes Consortium (SDOC) are widely utilized [2]. Its multifactorial etiology includes physical inactivity, malnutrition, inflammation, and hormonal decline [3,4]. The prevalence of this condition ranges from 9% to 40.4%, notably increasing in postmenopausal women due to estrogen deficiency [2, 5,6] and correlating with lower Sarcopenia – Quality of life (SarQoL) scores and muscle mass [7] Menopause accelerates sarcopenia through impaired muscle regeneration linked to reduced estradiol, which normally modulates inflammation (e.g., IL-6, TNF-α, IL-1β), oxidative stress, and satellite cell activation [8-10]. Estrogen receptor deficiency is associated with fewer satellite cells [11], while testosterone supports their activity [10]. These hormonal changes disrupt muscle-regulating pathways such as IGF-1, TGF-β and myostatin, increasing the risk of sarcopenia in post-menopausal women [3,12].

Osteosarcopenia is defined as the coexistence of sarcopenia and osteoporosis and it has a high prevalence among postmenopausal women (50–60%) [13]. It is associated with factors such as low BMI, reduced skeletal muscle mass, low handgrip strength, poor physical performance, low physical activity, and inadequate intake of protein and calcium. It has been observed that for every kilogram decrease in handgrip strength, the risk of osteosarcopenia can increase by as much as 16.2%, making this measure a practical tool for identifying at-risk women and promoting preventive interventions [13].

Diagnosis and assessment

The main scientific societies have proposed various diagnostic criteria for sarcopenia. The EWGSOP2 recommends a sequential approach, starting with the use of the SARC-F (Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls) questionnaire as a screening tool to identify probable cases, and low muscle strength as the initial point for diagnosis. Low muscle mass confirms the diagnosis, which is deemed severe if accompanied by low physical performance [1]. In contrast, the AWGS (adapted for Asian populations) highlights the gait speed test, grip strength, and muscle mass assessed through DXA or bioimpedance [14].

The International Working Group on Sarcopenia (IWGS) proposes defining sarcopenia as the combination of low muscle mass and low walking speed [15]. Meanwhile, the Foundation for the National Institutes of Health (FNIH) prioritizes muscle strength adjusted for body mass index, with cutoff points based on U.S. studies [16]. The Sarcopenia Definitions and Outcomes Consortium (SDOC) has concentrated almost exclusively on grip strength and gait speed, downplaying the diagnostic role of muscle mass [17] (Table 1).

Treatment

Pharmacological measures

Menopause Hormone Therapy (MHT):

As previously explained, skeletal muscle is an estrogen-related tissue. Prior studies have linked decreased estrogen levels to reduced lean mass, muscle atrophy, and poor physical performance [18-

[22]. MHT is not recommended for treating sarcopenia in postmenopausal women, as current evidence does not demonstrate significant improvements in muscle mass or strength [23-25].

Possible future therapeutic targets

Currently, there is a promising field of preclinical research exploring various targets for the treatment of sarcopenia in the general population: myostatin/activin inhibitors (trevogrumab, bimagrumab), GH/IGF-1 pathway modulators (ibutamoren, growth hormone, ghrelin, anamorelin), androgens (enobosarm, OMK0773, testosterone), mitochondrial enhancers (coenzyme Q10, nicotinamide riboside), and other agents like denosumab, MYMD1, or mesenchymal stem cells, all of which are still in developmental stages. Previous clinical studies testing anti-myostatin antibodies have demonstrated minimal results.

Therefore, no recommendations can be made regarding pharmacological treatments for the prevention or management of sarcopenia outside of a clinical trial setting. It is important to note that increases in muscle mass or strength do not necessarily translate into improvements in physical performance. Ongoing clinical trials will be crucial in determining their future role in clinical practice for postmenopausal women [26-30].

Non-pharmacological measures

Physical activity

Regular physical activity is recommended for postmenopausal women to enhance muscle mass and strength while reducing fat mass, irrespective of age or the duration of the intervention [31,32].

Combined aerobic and resistance exercise training

Aerobic exercise is particularly effective, as it induces fat loss, whereas resistance training is more advantageous for increasing strength and muscle mass. Moderate-intensity aerobic and resistance exercises lasting 8 weeks or more are recommended to benefit cardiorespiratory fitness and improve whole-body muscle strength. Exercises should be performed at least 3 times a week, and last, cumulatively, at least 150 minutes [31,33].

Exercise also improves quality of life [34] and metabolic profile, particularly when incorporating resistance training or high-intensity interval training [35]. Other modalities, such as functional training [36] or whole-body vibration [37,38], can provide additional benefits in strength, balance, and inflammation reduction.

Nutritional interventions

- **Protein supplementation:** Protein supplementation, particularly whey protein and leucine, may support muscle protein synthesis, its function and strength; however, long-term benefits remain inconsistent [39].
- **Others:** Other types of proteins, including soy protein, branched-chain amino acids, and isoflavones, have not demonstrated effects on lean body mass [32]. The timing of protein intake does not impact the increase of lean mass, strength, or physical performance in postmenopausal women engaging in resistance exercise [40].
- **Vitamin D:** In older adults with vitamin D deficiency, supplementation is recommended to enhance calcium absorption, lower PTH levels, and reduce the risk of falls and fractures [40-44]. For individuals over the age of 75, a dose of 2000-4000 IU/day is suggested, as the standard

dose may be inadequate [39]. Furthermore, low estradiol and vitamin D levels have been linked to reduced muscle mass, indicating a potential synergistic effect on musculoskeletal health [45-47].

However, the results of the studies in menopausal women are inconsistent; some have shown benefits of vitamin D on muscle strength and function [32,48], while others have not [49,50]. It is recommended to consider the use of calcifediol, as it has proven to be more effective and faster than cholecalciferol in raising serum levels of 25(OH)D [51,52]; moreover, it could lead to better functional outcomes in postmenopausal women [53]. Likewise, daily administration of vitamin D seems to be more effective than high single doses for improving muscle strength [54].

- **L-citrulline supplementation (CIT):** CIT has demonstrated an anabolic role in skeletal muscle, improving lean mass and strength, particularly when paired with resistance exercise or high-intensity interval training (HIIT) [55-58]. In postmenopausal women, its combined application with resistance or vibration training may increase muscle strength, lean mass, and endothelial function, even in those with obesity or hypertension [59,60].

- **Creatine supplementation:** Creatine supplementation may be beneficial for improving muscle strength in older women, particularly when taken for a minimum of 24 weeks. An increase in both upper and lower body strength has been noted, which could lead to improved functionality, quality of life, and a decreased risk of falls and fractures [61].

- **Magnesium:** Magnesium deficiency affects muscle metabolism; however, no impact has yet been demonstrated on muscle outcomes in postmenopausal women (muscle strength, muscle mass, or function) [39].

- **Omega-3 polyunsaturated fatty acids (PUFAs):** It is recommended that postmenopausal women consider including PUFAs in their diet, as they have anti-inflammatory effects and a potential anabolic role in muscle, which can be beneficial in treating sarcopenia. PUFA supplementation has improved walking speed, although not necessarily muscle strength [39].

- **Dairy products**: Dairies can be considered part of a nutritional strategy for sarcopenia in postmenopausal women. Regular or high-fat milk consumption has shown a stronger association with lean mass and muscle mass, likely due to the higher vitamin D content [62].

- **Diet pattern:** A Mediterranean diet rich in plant-based proteins and antioxidant nutrients (fiber, polyunsaturated and monounsaturated fatty acids, beta-carotene, vitamin C, magnesium, and flavonoids) is recommended, as it has been associated with bone mineral content, skeletal appendicular muscle mass and skeletal muscle mass index (SMI) in postmenopausal women [63].

Additionally, greater adherence to this diet is associated with increased muscle strength and lean mass. In contrast, pro-inflammatory diets, which are rich in flour and processed meats, are linked to an increase in inflammatory cytokines and a loss of muscle mass [64-66].

- High-risk alcohol consumption should be avoided, as it is associated with a greater risk of sarcopenia [67].

Nutritional and physical activity interventions

Engaging in regular physical exercise, including both mixed and resistance activities, is recommended to enhance muscle strength and to treat and prevent sarcopenia in postmenopausal women. While protein and carbohydrate supplementation related to training produces variable effects and mixed results on muscle strength [68], maintaining physical activity during weight loss is crucial for preserving muscle mass, as a hypocaloric diet may lead to the loss of both muscle and fat mass, increasing the risk of sarcopenia. The most effective strategy involves a combination of caloric restriction, physical exercise, and a protein-rich diet to reduce fat mass while maintaining or increasing muscle mass [69].

Recommendations and Key Messages

- HCPs should be aware that sarcopenia, a muscle disease characterized by loss of strength, mass, or physical function, is more prevalent in postmenopausal women due to estrogen deficiency. ⊕⊕⊕◯ B
- HCPs should be aware that the diagnosis of sarcopenia is based on various criteria according to different scientific societies, with the most widespread being that of the European Working Group on Sarcopenia in Older People (EWGSOP2): low muscle strength, low muscle mass and low physical performance. ⊕⊕⊕◯ A
- Assessment for sarcopenia should be combined with the identification of osteoporosis to enable appropriate diagnostic and intervention strategies. ⊕⊕⊕◯ B
- MHT is not recommended for treating sarcopenia in postmenopausal women, as current evidence does not demonstrate significant improvements in muscle mass or strength. ⊕⊕◯◯ C
- Non-pharmacological treatment with regular physical exercise (aerobic and resistance) is recommended as the most effective intervention for sarcopenia. ⊕⊕⊕◯ A
- Consider protein (whey and leucine), creatine or L-citrulline supplementation in addition to physical exercise for the management of sarcopenia, although long-term data are lacking. ⊕⊕◯◯ B/C.
- The role of other types of protein supplementation or magnesium is not well established and, therefore, is not recommended. KM
- HCPs should be aware that the effect of Vitamin D supplementation on sarcopenia is inconsistent, although benefits are observed regarding falls reduction and bone health. ⊕⊕⊕◯ A/B
- HCPs should be aware that the Mediterranean diet is associated with greater muscle mass and improved bone quality in postmenopausal women, whereas pro-inflammatory diets are linked to a higher risk of sarcopenia. ⊕⊕◯◯ A/B
- When implementing caloric restriction for weight loss, a protein-rich diet combined with regular physical activity is recommended to maintain muscle mass and avoid muscle loss. ⊕⊕⊕◯ A

Table 1. Diagnostic tools for sarcopenia – summary

Table 1. Diagnostic tools for sarcopenia according to various societies/consensus

Society/Consensus	Variables evaluated	Diagnostic criteria	Advantages	Disadvantages
EWGSOP2 *(Europe, 2019)*	Muscle strength (hand grip) Muscle mass (DXA or BIA) Physical performance (gait speed, SPPB)	Probable sarcopenia: low muscle strength Confirmed: low muscle mass Severe: poor physical performance	Progressive approach, clinical applicability, functional validity	Requires specific equipment (DXA, BIA), variability in cut-off points according to population.
AWGS *(Asia, 2019)*	Muscle strength (hand grip) Muscle mass (DXA, BIA) Physical performance (gait speed, chair stand-up test)	Sarcopenia: low muscle mass plus low muscle strength or poor physical performance.	Tailored to Asian populations, includes practical functional tests	Requires specific equipment Ethnic variability
IWGS *(International, 2011)*	Muscle mass (DXA) Gait speed	Sarcopenia: low muscle mass + gait speed < 1.0 m/s	Simplicity, focus on mobility	Does not include muscle strength assessment, possible underestimation of cases
FNIH *(USA, 2014)*	Muscle strength (manual grip) Muscle mass adjusted for BMI	Sarcopenia: low muscle strength plus low relative muscle mass	Criteria based on large cohorts, focus on functionality	Specific cut-off points for U.S. population, possible limitation in other populations
SDOC *(USA, 2020)*	Muscle strength (mainly manual grip) Gait speed	Sarcopenia: low muscle strength + reduced physical performance	Simplicity	Does not include muscle mass, possible underestimation

NOTE: EWGSOP2: European Working Group on Sarcopenia in Older People 2; **DXA:** Dual-energy x-ray absorptiometry; **BIA:** Bioelectrical Impedance Analysis; **SPPB:** Short Physical Performance Battery; **AWGS:** Asian Working Group for Sarcopenia; **IWGS:** The International Working Group on Sarcopenia; **FNIH:** Foundation for the National Institutes of Health; **USA:** United States of America; **BMI:** Body Mass Index; **SDOC:** Sarcopenia Definitions and Outcomes Consortium.

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8. Skin, Cartilage, Connective Tissues

Estrogen receptors, ERα and ERβ, are expressed widely in all connective tissue cells [1]. Many of these cell types also possess aromatase and other enzyme activity and therefore the ability to metabolise hormones. Estrogen indirectly increases the levels of collagen types I and III, elastin, glycosaminoglycans, and ezrin, a structural protein involved in maintaining the integrity of the skin barrier. Estrogen is able to influence cytokine production from many cells and reduces expression of pro-inflammatory cytokines and downregulates macrophage migration inhibitory factor which is known to delay healing [2-5]. Estrogen protects keratinocytes and fibroblasts from oxidative stress leading to an increase in pro collagen 1 synthesis [6]. Considering this data, we might expect the loss of estrogen at menopause which shall affect many aspects of connective tissue health. However, in comparison to the analysis of other changes at menopause, this area has been less extensively studied, and outcomes are misleading due to inconsistencies in study design.

Skin

60 to 70% of women at menopause report changes in their skin [7,8]. Menopause is associated with a 30% loss of skin collagen in the initial 5 years postmenopause and total collagen decreases at an average of 2.1%/post-menopausal year for 15 years [9]. Decreases in skin elastin content, hydration and peripheral microcirculation have also been documented after menopause [10,11]. Also wound healing capacity is reduced [12]. ERβ signalling appears to be a key suppressant of skin aging and its epidermal expression declines with age [13]. Aromatase activity in the skin allows conversion of DHEA into estrogen after menopause but DHEA synthesis declines with age contributing to the deficit in estrogens in the skin [14].

Limited randomized controlled studies have shown that subcutaneous, topical and oral estrogen therapy has beneficial effects to prevent collagen loss and increase skin thickness. Changes in the number and thickness of elastic fibres and skin elasticity are less significant [9,11,14-17]. Estrogen therapy reduces the likelihood of dry skin, and this may be due to effects on the levels of mucopolysaccharides, hyaluronic acid and dermal water content. Menopause hormone therapy improves the skin microcirculation. However, the effects of estrogen on wound healing remain unclear [10]. A small study which has shown a reduction in skin wrinkling with MHT only in non-photo-aged skin highlights the role of photoprotection in skin aging [18].

There are few studies examining the effect of progesterone used either topically or systemically. Some benefit on markers of skin aging has been reported. This includes skin elasticity, wrinkle depth, epidermal moisture, skin firmness and skin dryness. A possible mechanism of action is an effect of progesterone to suppress matrix metalloproteinases [19].

Hair

Data are lacking on the effect of menopause or menopause hormone therapy on hair health and its quality in post-menopausal women. Studies have demonstrated that estrogen alters the growth and life cycle of the hair follicles, it alters aromatase activity, prolongs the anagen phase of the hair growth cycle and increases the synthesis of growth factors [20]. With the reduction in estrogen at menopause, hyperandrogenism may appear and this can contribute to androgenetic patterns of hair loss in women and miniaturization of the hair follicle [21].

Joints

A putative role of estrogen in osteoarthritis was first suggested in 1925 but differences across studies in evaluation criteria, patient populations and MHT duration have led to conflicting results [22]. Gender differences in cartilage exist between men and women, and this is more evident in postmenopausal women who have lower cartilage volume and greater cartilage loss[23]. The role of reproductive factors and exogenous hormone supplements is complex and significant gaps in our knowledge persist.

Studies have confirmed that estrogen has a significant role in increasing proteoglycan production, reducing inflammation and reactive oxygen species and regulating calcium signalling in chondrocytes. It also regulates sub-chondral bone turnover [24]. Furthermore, sex hormones have been shown to modify the pain experience by modulating peripheral and central neural pathways [25,26]. However, data for an association of endogenous hormone and osteoarthritis are inconclusive.

Research has confirmed an association between menopause and increased joint pain [1]. In a systematic review and meta-analysis of 321 studies examining the global prevalence of symptoms reported by menopausal women, joint and muscle discomfort was the most cited symptom affecting over 65% of women [27]. This link is also seen with medications that are used to lower estrogen levels prior to menopause [28]. Several animal and pre-clinical studies have demonstrated protective effects on the cartilage deriving from the use of estrogen [29]. Postmenopausal women have thinner articular cartilage, and the use of estrogen replacement therapy / HRT has been shown to increase not just cartilage thickness but also the thickness of intervertebral discs [30, 31]. The Women's Health Initiative study (WHI) has shown greater relief of joint pain and stiffness and a reduced occurrence of new musculoskeletal symptoms in women taking MHT. A lower likelihood of hip arthroplasty surgery was seen in women taking estrogen replacement therapy, yet not in women on combined hormone therapy [32,33]. This raises the question of whether progesterone attenuates some of the benefit seen with estrogen use. Women who stopped MHT, subsequently experienced twice the rate of joint pain and stiffness compared to women stopping placebo treatment [34]. Most studies have failed to show any link between MHT and radiographic knee osteoarthritis or the need for knee arthroplasty [35].

Tendons

The effects of aging and estrogen deficiency on tendon health have been poorly investigated and results are misleading [36]. Age-related changes in tenocyte behaviour may result in less effective healing and an increased frequency of tendon injuries [37]. Stem cell populations and self-renewal potential appear to reduce with age [38]. However, the full impact of aging on tendon mechanical properties remains unclear. The impact of estrogen deficiency has been largely studied in animal models and these show links between a reduction in estrogen and reduced tendon tensile strength, collagen synthesis, fibre diameter and density, and increased degradation rates [36]. Replacing estrogen in postmenopausal women improves tendon structure and biomechanical properties [39,40]. Conflicting results are seen in trials combining exercise and menopause hormone therapy. This may reflect different exercise modalities used in the trials and different routes of estrogen administration. Oral estrogen, due to its impact on hepatic metabolism, may reduce the levels of growth factors involved in collagen synthesis during physical activity [41]. MHT plus exercise compared to placebo plus exercise led to greater condition improvements of women with trochanteric bursitis, but only if their BMI was less than 25 [42].

Connective tissue disease

There is a clear influence of gender on the incidence and prevalence of auto-immune diseases, with women being more likely to be affected by them [43-45]. At menopause a number of changes in neutrophil percentage, lymphocyte numbers and reductions in the cytotoxic activity of natural killer cells lead to an increased risk of lymphocyte mediated autoimmune disease [46]. There are reproducible increases in production and responsiveness to inflammatory cytokines such as IL-1, IL-6 and TNFα [47]. While there is a clear impact of hormone factors on rheumatological health, there is also a complex interplay of other factors, including aging.

Systemic lupus erythematosus:

Early menopause and a surgical menopause have been associated with an increased risk of systemic lupus erythematosus (SLE) [48]. Some studies have shown a reduced frequency of exacerbations after menopause, but this may be linked to aging rather than menopause itself [49-52]. However, despite the reduced exacerbations, there appears to be a greater accumulation of damage after menopause. Observational and retrospective studies of MHT use in women with SLE have not shown any increase in disease activity or an increase in cardiovascular complications [53]. One RCT has shown that MHT may increase the risk of mild to moderate flares in SLE activity but does not alter the frequency of severe episodes [54]. From a practical perspective, care needs to be taken with the use of MHT in women with antiphospholipid antibodies because of the increased risk of coagulation disorders [55].

Rheumatoid arthritis:

Early menopause may be associated with an increased risk of rheumatoid arthritis (RA) and menopause generally with an increased risk of disease progression [56-58]. The peak incidence of RA coincides with menopause [59]. The WHI has suggested that MHT may be protective in women with RA but this was a non-significant change. There appeared to be no difference in disease activity in women with RA taking MHT [60]. In a small randomized controlled trial (RCT) of 88 postmenopausal women, the use of MHT reduced clinical and laboratory signs of RA activity; bone and cartilage turnover was reduced as well [61,62].

Fibromyalgia:

Fibromyalgia, the pathogenesis of which remains poorly understood, frequently emerges at mid-life, and many of the symptoms overlap with those of the menopause transition. However, pain and tenderness appear to increase in postmenopausal women with fibromyalgia compared to their premenopausal peers, suggesting a causal link [63, 64]. There is little data on the role of MHT in women with fibromyalgia and results are often conflicting. The studies are generally small, and follow-up is short.

Recommendations and Key Messages

- Estrogen receptors are widely expressed across all connective tissues. ⊕⊕⊕⊕ KM
- Estrogen deficiency is associated with adverse changes in skin, hair and tendon composition and quality. ⊕⊕⊕◯ KM
- Estrogen deficiency is associated with increased joint pain and thinning of articular cartilage. ⊕⊕◯◯ KM
- Ovarian hormones may have a role in the presentation, severity and progression of auto-immune diseases such as SLE and rheumatoid arthritis. ⊕◯◯◯ KM
- The quality of the studies published to date examining the impact of sex hormones on connective tissues and autoimmune dysfunction is low and recommendations for treatment cannot be drawn from the currently available data. GPP

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9. Cardiometabolic

Cardiovascular disease is the principal cause of morbidity and mortality in postmenopausal women. In addition to standard cardiovascular risk factors that have greater impact on women than men, such as central obesity [1], diabetes mellitus/insulin resistance [2], and triglyceride-rich lipoproteins [3], several conditions specific to women have been recognized as important contributors/risk factors to cardiovascular disease. These include premature ovarian insufficiency (<40 years), gestational diabetes, hypertensive disorders of pregnancy such as preeclampsia, preterm delivery, polycystic ovary syndrome, and inflammatory/autoimmune disorders, which disproportionately affect women [4,5]. Major primary prevention measures are smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise and diabetes and lipid control (see section 3 Lifestyle) [6]. Primary prevention strategies which are effective in men, namely the use of aspirin and statins, do not afford a protective effect for coronary disease, cardiovascular mortality or all-cause mortality in women [7-9].

Menopausal hormone therapy (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 [10].

There is strong and consistent evidence that estrogen therapy is cardioprotective when started around the time of menopause (often referred to as the 'window of opportunity' or 'timing' hypothesis) and has no beneficial effect when started more than 10 years after menopause [10,11]. In the 13-year follow-up of women in the Women's Health Institute (WHI), the cumulative data (intervention and follow-up phases combined) in the 50–59-year-old age group showed a reduction of coronary heart disease (CHD) (hazard ratio (HR) 0.65; 95% CI 0.44–0.96) in the women receiving conjugated equine estrogens (CEE). The risk of myocardial infarction was also significantly decreased (HR 0.60; 95% CI 0.39–0.91) [12]. In this age group, the women receiving conjugated equine estrogen–medroxyprogesterone acetate (CEE + MPA) in the WHI trial did not show a CHD benefit (HR 1.27; 95% CI 0.93–1.74). Women <10 years since menopause who received CEE + 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 regimen using a continuous progestogen [12].

Meta-analyses of randomized controlled trials (RCTs), including data from the WHI, have shown a significant reduction in CHD as well as in all-cause mortality in women under the age of 60 treated with estrogen [13-15]. In the WHI, the cumulative results showed a reduction in all-cause mortality in the 50–59-year-old age group with CEE alone and CEE+MPA, although the point estimates just missed statistical significance (RR 0.78; 95% CI 0.59–1.03 for CEE alone; RR 0.88; 95% CI 0.70–1.11 for CEE+MPA) [12]. When mortality data for CEE and CEE + MPA from the two WHI trials during the intervention phase were combined, the reduction in all-cause mortality was significantly reduced by 31% (95% CI 6-49%) [16]. Several meta-analyses have shown similar findings [13-15,17,18]. In the Cochrane analysis, women initiating MHT 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) [19]. Despite this, the 2022 USPSTF recommendation continues to advise against the routine use of MHT for the primary prevention of chronic conditions, including cardiovascular disease in asymptomatic menopausal women, citing potential harms that may outweigh the benefits at the population level [20]. An observational study from Finland using the National Death Index reported that estradiol products (oral

and transdermal) with and without progestogen decreased coronary and all-cause mortality significantly (12–54%). It should be noted that while the reductions of CHD and all-cause mortality risks were linked to the duration of the hormone therapy (HT), the age at initiation did not make a significant difference [21].

Additional long-duration longitudinal observation studies consistently show that MHT reduces all-cause mortality [22]. In a recent Danish observational study linked to the nationwide death registry, postmenopausal HT mortality was statistically significantly lower than that of the background population (HR 0.83; 95% CI 0.78-0.89) before 2002, when systemic use of HT was prevalent. After publication of the WHI in 2002, as HT prevalence decreased and its non-systemic use increased, postmenopausal HT mortality benefit dissipated and was no longer statistically different from that of the background population (HR 1.02 95% CI 0.94-1.11) [23].

The Danish Osteoporosis Prevention Study (DOPS) is the only trial in which participants mirrored women of observational studies from which the estrogen cardioprotective hypotheses was generated. In DOPS, women were on average 50 years of age and 7 months from menopause when randomized prospectively to receive standard doses of estradiol and norethisterone in an open-label fashion, or no treatment, for 10 years and with 16 years of follow-up [24]. There were statistically significant reductions in all-cause mortality and in hospitalizations for myocardial infarction and congestive heart failure.

The Early versus Late Intervention Trial with Estradiol (ELITE) is the only *a priori* designed RCT to test the timing hypothesis of HT [25]. In ELITE, the effects of oral estradiol 1 mg + vaginal progesterone 45 mg (for women with a uterus) and placebo in two groups of women, one <6 years from menopause and the other $\geq$10 years from menopause, showed a reduction in carotid artery intima-media thickness over time in the younger women, and no change in the older women, validating the timing hypothesis. ELITE results show that the timing of estrogen therapy is important in influencing the progression of cardiovascular disease [25].

At lower than standard doses of HT, the Kronos Early Estrogen Prevention Study (KEEPS) did not show a difference between CEE 0.45 mg, transdermal estradiol 0.05 mg and placebo on carotid artery intima-media thickness and coronary artery calcium [26], consistent with the known dose-response effect of HT on carotid artery intima-media thickness [27]. In WHI, standard dose of CEE at 0.625 mg daily statistically significantly reduced coronary artery calcium in women receiving HT [28].

Initiation of MHT in elderly women (>60 years old) or those who are more than 10 years postmenopausal does not appear to reduce the risk of coronary events [19]. The cumulative 18-year data of the WHI and the Cochrane analysis did not show a significant increase in CHD or mortality in the older age groups [16,19]. There was an increase in venous thrombosis and stroke with initiation of oral MHT in the older age groups [12,19]. 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 [29].

Diabetes mellitus deserves special attention as it has immense morbidity and mortality implications for women. Approximately 70-80% of individuals with diabetes succumb to cardiovascular disease and women with diabetes have greater cardiovascular morbidity than do men [30-32]. Diabetes is one of the only cardiometabolic risk factors known to eliminate premenopausal cardioprotection. The cardiovascular health implications of diabetes are especially relevant after menopause, in which insulin resistance, glucose intolerance, and new onset of diabetes all increase [33]. MHT improves

insulin resistance and glucose intolerance and statistically significantly reduces new onset diabetes mellitus by 30% when compared to placebo [34-39].

MHT has been demonstrated to provide beneficial long term effects on multiple cardiovascular biomarkers, such as total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and lipoprotein(a) [40]. Oral estrogen increases triglyceride concentrations [40], which is thought to be due to first pass metabolism in the liver, a finding not observed with transdermal estrogen [26]. Although elevated triglycerides levels are generally considered a negative effect of MHT, recent findings suggest that MHT actually reduces atherogenic triglyeride rich lipoproteins, including total and small very low-density liporprotein (VLDL), as well as intermediate density lipoprotein (IDL) particles [41]. Importantly, the increase in triglycerides with oral MHT reflects triglyceride enrichment of LDL and HDL rather than VLDL and IDL, which are the primary triglyceride transporters in plasma [41].

MHT in women with prior cardiovascular disease or uncontrolled risk factors has been approached with caution, but recent evidence suggests that it does not increase the risk of cardiac events in secondary prevention populations [42]. This is supported by a 2024 systematic review and meta-analysis including 23 RCTs, which found no secondary prevention benefit but showed no significant increase in myocardial infarction, stroke, cardiac death among women randomized to MHT. Transdermal estrogen, which may carry a lower risk of thrombosis [43] and inflammation [43,44] compared to oral therapy, may be a reasonable option for symptom relief in women with uncontrolled cardiovascular risk factors such as hypertension, diabetes, or hyperlipidemia, particularly when initiated at a younger age or near the onset of menopause.

Recommendations and Key Messages

- Certain cardiovascular risk factors are unique to or disproportionately affect women, especially diabetes mellitus. Unique risk factors include early menopause or POI, hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, polycystic ovary syndrome and autoimmune diseases. Assessment of these sex-specific factors is essential for accurate cardiovascular risk stratification. ⊕⊕⊕◯ A
- In women aged under 60 years who are recently postmenopausal and without cardiovascular disease, estrogen therapy reduces CHD and all-cause mortality. Multiple analyses, including the Cochrane review, meta-analyses and WHI 18-year follow-up, show consistent mortality benefits when HT is initiated before age 60 years or within 10 years of menopause. ⊕⊕⊕⊕ A
- The daily continuous combined oral CEE+MPA data are less comprehensive, but other combined therapy regimens appear to be cardioprotective, as shown in the Danish and Finnish studies. ⊕⊕⊕◯ A
- We recommend that HCPs consider the potential benefits of estrogen/MHT for the reduction of all-cause mortality and prevention of CHD in their decision making when initiating MHT in healthy postmenopausal women below age 60 years or within 10 years of menopause onset. Use of MHT solely for primary prevention of CHD is “off label”. GPP
- MHT reduces the incidence of new-onset diabetes, and this advantage should be considered alongside other preventive effects of MHT, such as reduction of osteoporosis, bone fracture, colon cancer, CVD and all-cause mortality in women aged under 60 years of age with no evidence of CVD. ⊕⊕⊕◯ A
- MHT should not be used for secondary prevention but does not appear to increase the risk of CVD events. ⊕⊕⊕◯ B
- Transdermal estrogen, due to a lower risk of thrombosis and inflammation, may be a reasonable option for symptom relief in women with uncontrolled cardiovascular risk factors. ⊕⊕◯◯ B
- The recent removal of “black box” warnings for “HRT” by the US Food & Drug Agency (FDA) accentuates the benefits versus risks ratio to which the cardiometabolic benefits are a major contributor. KM

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10. Coagulation: Venous Thromboembolism (VTE)

Epidemiology

Venous thromboembolism (VTE) is the most prevalent serious adverse effect of oral MHT in postmenopausal women [1]. The incidence of VTE (both deep vein thrombosis (DVT) and pulmonary embolism (PE)) in women on MHT is one or two cases per thousand woman-years. Evidence from early randomized controlled trials (RCTs) and extensive observational studies shows a 2 to 4-fold increased risk of VTE associated with oral MHT [2,3]. The VTE risk is further increased by risk factors such as age (particularly after 60 years), personal or family history of VTE, thrombophilia and obesity. Temporary risk factors, such as surgery or hospitalization, may also contribute to the risk. The VTE risk associated with oral MHT is front-loaded, peaking in the first year and diminishing with continued use. If MHT is stopped, VTE risk returns to the baseline within months [4].

- Oral MHT is associated with a 2 to 4-fold increased risk of VTE.

MHT and coagulation

Oral estrogen has been shown to affect procoagulant and anticoagulant pathways, as well as fibrinolysis. This results in a procoagulant state typified by activated protein C resistance and increased fibrinolytic markers such as D-dimer. When taken orally, estrogen is converted to estrone in the intestine and liver, which affects hepatic coagulation protein synthesis and tilts the haemostatic balance towards hypercoagulability. Transdermal administration of estrogen bypasses this first-pass metabolism and consequently does not significantly impact coagulation. The most compelling evidence for this difference in prothrombotic risk comes from studies of thrombin generation. Thrombin converts fibrinogen to fibrin in the final step of clot formation. Thus, the assessment of thrombin generation gives a global overview of the interaction of all the coagulation factors in the cascade and is considered a good laboratory marker of thrombotic risk.

All the parameters of thrombin generation were increased in women taking oral MHT, but women taking MHT containing transdermal estradiol were no different from non-users [5]. Estrone levels correlated with peak thrombin generation in women taking oral MHT, but no correlation was observed in those using MHT containing transdermal estradiol. This finding was corroborated in a further study, which showed that oral estrogens increased thrombin generation in a dose-dependent manner and that the effect of transdermal estrogen was dependent on the progestogen type [6]. Thrombin generation in women receiving MHT containing transdermal estradiol was increased in combination with progestins but was no different from non-users in combination with micronized progesterone.

Of interest, anticoagulation has been shown to mitigate the VTE risk in women on hormonal therapies. Analysis of a subgroup of women receiving hormonal therapies in a large RCT of anticoagulation for VTE showed that hormonal therapy did not increase the risk of recurrent VTE in women on therapeutic anticoagulation [7].

- Laboratory studies show that oral estrogen causes hypercoagulability, but transdermal estrogen has a neutral effect.

- Women with acute VTE who take hormonal therapy can safely continue this while on therapeutic anticoagulation. This gives the option for considered review of the hormonal treatment instead of abrupt discontinuation.

MHT Characteristics

MHT containing oral estradiol versus MHT containing transdermal estradiol

The most critical determinant of VTE risk relating to MHT is the route of administration. Much of the historical evidence for MHT-related VTE risk relates to oral MHT, particularly the combination of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA). This risk was evident in the Women's Health Initiative (WHI) study and confirmed in numerous observational studies [8]. The ESTHER case-control study was the first to show that transdermal estrogen did not increase the risk of VTE, and this finding was supported by subsequent case-control and cohort studies [9]. Canonico's systematic review and meta-analysis highlighted the increased risk associated with oral estrogens and the absence of risk associated with transdermal preparations [4].

The safety of MHT containing transdermal estradiol concerning VTE risk was further confirmed using observational data from large healthcare datasets. Data from the Million Women Study showed increased VTE risk in users of oral estrogen-only MHT (RR 1.42, 1.22-1.66) and oral estrogen-progestin MHT (RR 2.07, 1.86-2.32) but no evidence of an increased risk of VTE for current users of transdermal estrogen-only MHT (RR 0.82, 0.64-1.06) [10]. A recent UK study comprised nested case-control studies using two primary care research databases with data from 1998 to 2017 [11]. They included 5795 women with VTE and 21760 controls, with exposure to MHT within 90 days of the index date. The majority were on oral MHT, which was associated with a significantly increased risk of VTE (OR 1.58; 1.52-1.64) for both estrogen-only preparations (OR 1.40, 1.32 -1.48) and combined preparations (OR 1.73, 1.65-1.81). MHT preparations containing transdermal estradiol were not associated with an increased risk of VTE, a finding consistent across different regimens (adjusted OR, 0.93; 95% CI, 0.87-1.01). A US study nested case-control study examined hormone-associated VTE risk in commercially insured women aged 50 to 64 [12]. For exposures within 60 days, oral MHT nearly doubled the risk of VTE compared to MHT containing transdermal estradiol (OR 1.92, 1.43-2.60). Transdermal risk did not increase risk compared with no exposure (unopposed OR 0.70, 0.59-0.83; combined OR 0.73, 0.56-0.96).

Choice of estrogen

The risk of VTE is increased with all oral estrogens. Higher doses of oral estrogen were associated with higher VTE risk [11,13,14]. Across all datasets, CEE, with or without MPA, is associated with the highest VTE risk. In the Vinogradova study, estradiol had a lower risk than CEE for estrogen-only preparations (0.85, 0.76-0.95) and combined preparations (0.83, 0.76-0.91) [11]. CEE + MPA had the highest risk (2.10, 1.92-2.31), and estradiol with dydrogesterone had the lowest risk (1.18, 0.98-1.42). In the Weller study, the risk was highest for oral MHT combinations with ethinyl estradiol, followed by CEE (ethinyl estradiol-CEE OR 1.55, 1.07-2.25) and lowest for estradiol (CEE-estradiol, OR 1.33, 1.02-1.72) [12].

Combined MHT and choice of progestogen

VTE risk is higher with combined MHT compared to estrogen-only MHT. In the WHI study, the risk of PE was significantly increased in the CEE + MPA arm (HR 1.98) compared with the placebo arm but not in the CEE-alone arm (HR 1.35) [15]. In a US case-control study, the use of estrogen in combination with

progestin was associated with increased VTE risk compared with estrogen alone (OR 1.60, 1.13-2.26) [13]. Similar findings were reported in the Million Women Study [10].

The higher VTE risk associated with progestogens in combined MHT is not a class effect. The choice of progestogen is also an important determinant of VTE risk, with micronized progesterone (OR 1.7) and pregnane derivatives (OR 1.9) being safe in the ESTHER study and norpregnane derivatives (OR 3.9) associated with an increased VTE risk [16]. The E3N Cohort Study also found norpregnanes were associated with increased thrombotic risk (HR 1.8, 1.2-2.7) and no significant thrombotic risk associated with micronized progesterone (HR0.9, 0.6-1.5), pregnanes (HR 1.3, 0.9-2.0) and nortestosterones (1.4, 0.7-2.4) [17]. Of note, very few women amongst those on pregnane derivatives in these observational studies were using MPA.

In a meta-analysis examining VTE risk with oral versus transdermal estrogen and progestogens, women taking transdermal estrogen with micronized progesterone did not have an increased risk (RR 0.93, 0.65-1.33) but norpregnanes were associated with increased VTE risk (RR 2.42, 1.84-3.18) [18]. A recent systematic review examining the effect of micronized progesterone on thrombotic risk as a component of combined MHT confirmed a neutral effect [19].

- Observational studies show that MHT containing transdermal estradiol, unlike oral MHT, does not increase the risk of VTE. In combination MHT, progestogens may contribute to the VTE risk; micronized progesterone and levonorgestrel-releasing intrauterine system are safe options.

Patient Characteristics

Age and obesity

The most common risk factors for VTE are advancing age and raised body mass index. The WHI data revealed an increase in background risk of VTE with each decade after the age of 50 years, and in combination with oral MHT this risk was exaggerated, with approximately a doubling of the risk in the placebo arm [8]. Raised body mass index is a well-accepted risk factor for VTE, and the combination of raised BMI and oral MHT markedly increased VTE risk (pooled OR 5.4, 2.9-10.0) compared to raised BMI alone (pooled OR 2.6, 2.1-3.3) in the Canonico meta-analysis. In the EStrogen and THromboEmbolism Risk (ESTHER) study, MHT consisting of transdermal estradiol use in women with raised BMI did not increase VTE risk above the background risk, and this has been confirmed in subsequent large observational studies [10,11].

Personal history of VTE

Previous VTE is the most significant risk factor for further VTE, particularly if the index episode was unprovoked. The Estrogen in Venous ThromboEmbolism Trial (EVTET) study was prematurely terminated due to an increased risk of recurrence in women taking combined oral MHT (estradiol/norethisterone), with VTE incidence of 10.7% and 2.3%, respectively, in both the MHT and placebo groups [20]. In the Menopause, Estrogen and Venous Events (MEVE) cohort study, 130 women with a history of VTE used MHT (mainly transdermal). The investigators concluded that transdermal estrogen, unlike oral estrogen, did not appear to cause recurrent VTE [21]. A recent UK retrospective cohort study included 115 women with a history of thrombosis (81% VTE, 19% arterial events) who were exposed to MHT containing transdermal estradiol for at least one year [22]. No recurrent events were recorded. While the sample size was modest, the results provided additional reassurance about the safety of prescribing transdermal estradiol to women considered at high risk.

Inherited thrombophilia

The two common inherited thrombophilias, factor V Leiden and the prothrombin G20210A mutation are predominantly found in individuals of European ancestry, and testing is seldom informative in other populations. The evidence relating to thrombophilia is derived from the WHI trials and case-control studies, such as ESTHER or the Oxford study [4]. In the meta-analysis by Canonico et al., the pooled odds ratio (OR) for VTE risk in individuals carrying one prothrombotic mutation was 3.3 (2.6-4.1) and in combination with oral estrogen, 8.0 (5.4-11.9). ESTHER was the only study that examined the effects of transdermal estrogen in combination with thrombophilia. They found an OR of 3.9 (2.6-5.9) associated with thrombophilia alone and an OR of 25.5 (6.9-95.0) in combination with oral estrogen [23]. Transdermal estrogen, with an OR of 4.4 (2.0-9.9), did not confer an additional risk beyond the baseline risk of thrombophilia alone. The use of MHT containing transdermal estradiol provides a safe option for people with potentially increased VTE risk, for example those with a personal or family history of VTE or thrombophilia, removing the need for thrombophilia testing.

- In individuals taking MHT, patient characteristics such as previous VTE, thrombophilia or obesity may further increase the VTE risk.
- MHT containing transdermal estradiol provides a safe option in individuals with increased VTE risk and, in those requiring combined MHT, may be combined with a suitable progestogen such as micronized progesterone.

Recommendations and Key Messages

- Individuals at increased risk for VTE include those with obesity, inherited thrombophilia or a previous history of VTE. KM
- Individuals requiring MHT should be risk assessed and counselled about their risk of VTE. GPP
- Oral estrogen therapy increases the risk of VTE and is not recommended in women at increased risk for VTE. ⊕⊕⊕⊕ A
- Unlike oral estrogen therapy, transdermal estrogen therapy does not increase the risk of VTE, even in the presence of additional risk factors such as obesity, inherited thrombophilia and previous history of VTE. ⊕⊕⊕◯ B
- Transdermal estrogen is recommended for use in high-risk women requiring MHT, in combination with a suitable progestogen in women with an intact uterus. ⊕⊕⊕◯ B
- For combination therapy, the choice of progestogen is important; the use of suitable progestogens is recommended, such as micronized progesterone, dydrogesterone, or a levonorgestrel-releasing intrauterine system. ⊕⊕⊕◯ B
- There is no indication for thrombophilia testing before commencing MHT. GPP
- There is no indication for routine anticoagulation as prophylaxis in women starting MHT. GPP
- In women who develop VTE while taking oral MHT, immediate discontinuation of MHT is not required while the individual is on anticoagulation. ⊕⊕⊕◯ B

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11. Central Nervous System (including Dementia)

For each section, consideration was given to previous position statements from the IMS [1] and The Menopause Society [2]. To ensure inclusion of subsequent clinical trials, we conducted a review of studies, published since 2022, on menopausal hormone therapy (MHT) and key outcomes (Alzheimer's disease, Parkinson's disease, stroke, migraine) in peri- and postmenopausal women. Abstracts were screened and carefully filtered, excluding the following: basic science (i.e., animal models), breast cancer research, reviews, books, systematic reviews, non-English papers, commentaries, retracted papers, study protocols, or, published prior to 2022. Texts were excluded at the full-text stage if they were not relevant to the specific neurologic disease, to hormone therapy, did not use validated or standardized outcomes, had a hormone therapy treatment time of <4 weeks, evaluated non-systemic hormone therapy only, evaluated hormone therapy with an additional pharmaceutical intervention, included premenopausal women only, or used mixed hormone therapy (except estrogen with progesterone).

Alzheimer's disease

The Women's Health Initiative Memory Study (WHIMS) is the only randomized, placebo-controlled trial of menopausal hormone therapy (MHT) for the primary prevention of dementia. That trial focused on all-cause dementia rather than Alzheimer's disease (AD) alone and was conducted in women who commenced MHT aged 65 years or older. Results from WHIMS indicated that conjugated equine estrogen plus medroxyprogesterone acetate (CEE+MPA) doubled the risk of all-cause dementia after an average follow-up of 4.05 years [3], whereas CEE had a neutral effect after an average follow-up of 5.21 years [4]. Most dementia cases in WHIMS were AD cases. The effects of CEE and CEE+MPA on death from AD or dementia were later studied in 27,347 WHI participants after an average follow-up of 18 years [5]. CEE+MPA was not associated with death from AD or dementia, while CEE alone was associated with a 26% lower risk of those conditions, an effect driven by the group of women aged 70-79 years at baseline. Based on the 18-year follow-up data, the number of women needed to treat to prevent one case of dementia with CEE was 2004, limiting the clinical relevance of that finding [6].

Women who experience early menopause due to premenopausal bilateral oophorectomy show increased mortality due to dementia [7]. As AD is the most common type of dementia, it is important to consider the use of MHT for prevention of dementia in this population. There are no randomized trials of MHT on the risk of AD or dementia in women with early menopause. However, observational studies show a decreased risk of dementia with the use of estrogen therapy (ET) in women with early menopause. Initial observational findings from the Mayo Clinic found an increasing risk of dementia with younger age at oophorectomy; that risk decreased with post-surgical ET use [8]. These findings were later replicated in a Danish cohort study [9]. Together, these observational studies show that early menopause is associated with an elevated risk of dementia, and that ET use can mitigate that risk.

Observational studies provide conflicting evidence regarding the effect of MHT on AD risk in naturally menopausal women. Several studies show increased risk [10–15], while others show the opposite [16–18] or no effect [19]. In general, earlier observational studies suggested a lower risk of AD with MHT, and more recent studies suggest its harmful effects [20]. Meta-analyses of these observational studies also provide conflicting findings, in part due to the extraction of different estimates of risk from the same studies [21–23]. It has been suggested that conflicting findings may be partially explained by differences

in MHT formulations, timing of hormone initiation, duration of use, and interaction with other reproductive factors. However, there are no randomized trials to improve understanding of these factors, and larger scale observational studies show no consistent findings regarding these factors.

The "critical window hypothesis" or "timing hypothesis" suggests that the effects of MHT on AD risk may depend on the timing of initiation of MHT in relation to the final menstrual period or age, with more favorable effects observed with early initiation of MHT and more harmful effects observed with later initiation [24]. Earlier observational studies favored this hypothesis [16,25], while more recent studies provide no support for it [13–15]. Counter to the timing hypothesis, the 15-year WHI follow-up data showed a reduced risk of death from all-cause dementia in women randomized to CEE at ages 70-79, but not in the 50-59 or 60-69 age groups [5].

In studies finding an elevated risk of AD with MHT, the magnitude of risk is smaller than the 2-fold increased risk observed in WHIMS. For example, a case-control study of 84,739 patients with AD and a similar number of control women from Finland, examined the association of MHT with AD risk overall and by MHT formulations, timing of initiation, and duration of use [11]. They found the risk to range from 9-17%, translating to 9 to 18 excess diagnoses of the disease per year in 10,000 women 70-80 years of age. In a nationwide nested case-control study from Denmark involving 61,475 women, MHT was associated with a 22% increase rate of AD [15]. In a nationwide longitudinal cohort study from Taiwan involving 105,072 women, MHT was associated with a 20% increased risk of AD [14].

Overall, the state of the current literature suggests that there is no reason to initiate MHT for the primary prevention of AD in naturally menopausal women, but for premenopausal women who undergo oophorectomy, ET may help prevent AD [26,27].

Parkinson's disease

The higher incidence and prevalence of Parkinson's disease (PD) in men, observed consistently in epidemiologic studies, suggests that women may have a protective characteristic, and ovarian hormones, especially estrogens, are a strong candidate. A number of reviews have summarized the preclinical studies suggesting that estrogens may have antiapoptotic and antioxidant effects, in addition to inhibiting the stabilization and aggregation of alpha-synuclein fibrils in the brain [28–30].

Women who experienced earlier menarche, later menopause, and longer duration of fertile life have a lower risk of PD, suggesting possible protective effects of endogenous estrogens or other ovarian hormones [31]. In some women who develop PD before menopause, PD symptom severity may worsen during the menstrual phase, when estrogen levels are lowest. Two recent cohort studies showed that women who underwent bilateral oophorectomy before reaching spontaneous menopause had an increased risk of PD [32,33]. Finally, some observational studies suggest that estrogen therapy may alleviate PD symptoms in the early stages of the disease [28].

The effects of MHT on PD remain controversial. A 2020 systematic review of 5 observational studies reported a reduced risk of PD in women who received MHT after menopause [23]. However, another 2020 systematic review of 10 observational studies did not confirm the MHT-PD association and reported an increased risk of PD in women who received estrogen-progestogen therapy and progestogen alone therapy [21]. Finally, a 2023 cohort study from South Korea showed an increased risk of PD in women who received estrogen alone, tibolone, or combined estrogen-progestogen therapy [34].

In contrast to this relatively coherent body of preclinical and observational studies, the evidence from clinical trials is limited. Some small trials have demonstrated mild efficacy of low-dose estrogens in improving motor disability and motor fluctuations in postmenopausal women, but estrogens have never been tested in large, long-term clinical trials of PD patients [30]. The risk of PD increases rapidly with advancing age after the age of 60 and women with PD are at increased risk of developing dementia. Given the recognized adverse effects of starting estrogen therapy after the age of 60 and the association of estrogen therapy with increased risk of dementia, estrogen is not a viable treatment for PD [35]. Therefore, in a recent NEJM review, estrogen was not mentioned as a current or potential therapy for PD [36]. Selective estrogen receptor modulators have been suggested as a possible alternative [35].

The use of estrogen therapy is less controversial for women who underwent spontaneous or iatrogenic premature (<40 years) or early menopause (40-44 years). In these women, the use of estrogen replacement therapy has been recommended for the prevention of several chronic conditions caused by estrogen deprivation (or hypo-estrogenicity), including PD. Clinical trial evidence is lacking, however, observational studies of large cohorts followed historically suggest that estrogen replacement therapy may reduce the risk of PD and parkinsonism in women who underwent premature or early menopause [32,33,37].

Stroke

Two systematic reviews and meta-analyses of RCTs and observational studies showed that menopausal hormone therapy (MHT) increases the risk of stroke, with one finding an overall 24% increased risk (RR 1.24, 95% CI 1.10 to 1.41) [38], and another finding a 14% increased risk (RR 1.14, 95% CI 1.04–1.25) [39]. However, both concluded that the risk depends on the timing of initiation, with null effects of MHT on stroke incidence when initiated fewer than 10 years after menopause onset or before 60 years of age, and an increased risk of stroke for women who initiate MHT more than 10 years after menopause onset or at age 60 years and older [38,39]. The increased risk was 21% in one study (RR 1.21, 95% CI 1.06-1.38) [38], and 17% in the other (RR 1.17, 95% CI 1.01-1.37) [39]. In a meta-regression analysis that specifically examined the timing hypothesis, data from 18 randomized clinical trials showed that MHT was associated with higher odds of a composite measure of incidence stroke, transient ischemic attack, and systemic embolism compared to placebo regardless of timing of initiation, with increasing risk as average age increased [40]. Randomized trials to date primarily comprised North American and European populations, demonstrating a need for high-quality randomized trials evaluating racial and ethnic differences in the effects of MHT on stroke outcomes.

Furthermore, observational studies suggest that the risk of stroke may vary depending on the route of administration, dosage, and formulation of MHT. Higher incidence of stroke may be specific to oral MHT rather than transdermal MHT, and risk may increase as dosage increases [41,42]. Other studies found that CEE was associated with higher stroke risk compared to estradiol therapy [43] and that tibolone may confer greater risk compared to no MHT use [44–46].

Migraine

Migraine is more common in women than men [47], commonly occurring during periods of estrogen withdrawal, including premenstrual withdrawal. Similarly, migraine becomes more common in the early perimenopause, likely because luteal phase levels of estradiol are higher in the perimenopause

compared to premenopause, resulting in a larger premenstrual withdrawal from estrogen [48]. Migraine improves in the postmenopause when estrogen levels stabilize.

There are two general categories of migraines, migraines with aura and migraines without aura. This distinction is important when considering the benefit-risk profile of estrogen-containing medications. For women with migraine with aura, oral estrogen-containing HT and oral contraceptives are associated with an increased risk for stroke. For women with migraine with aura, neurokinin-targeted therapies (e.g., NK3 antagonist, NK3/NK1 dual antagonist), other non-hormonal therapies (e.g., SSRIs, SNRI, low-dose paroxetine) and high-dose progesterone only pills (e.g. desogestrel 75 mcg dose) are effective and generally safer alternative treatments for menopause-related VMS [49].

Many women experience a worsening of migraine without aura during the perimenopause. In the perimenopause, continuous combined hormonal contraception and progestin-only contraception can prevent migraine through suppression of ovulation resulting in stabilization of estrogen levels and prevention of estrogen withdrawal [48,50]. For perimenopausal women with migraine without aura, estradiol- or estetrol-containing oral contraceptives or continuous transdermal estradiol are preferred to ethinyl estradiol-based oral contraceptive regimens because of their more favorable thromboembolic profiles. Doses of continuous transdermal estradiol must be sufficiently high to suppress ovulation. Combined oral contraceptives should be avoided in perimenopausal women with other vascular risk factors and should be stopped in women who develop migraine after initiation. MHT in typical doses or administered non-continuously is not recommended to treat migraine in the perimenopause because it does not minimize fluctuations in estrogen [51].

There are no randomized trials of MHT on migraine in postmenopausal women. Two large observational studies in postmenopausal women suggest that MHT increases migraine [52–54]. The route of administration and dose are important, as sustained-release forms of estrogen (transdermal patches, gels, sprays, etc.) provide more stable estrogen levels compared with oral routes which may worsen migraine symptoms [48,55]. Transdermal formulations are also preferable to oral formulations due to their more favorable thromboembolic profiles [48]. Tibolone was found to be a more effective option than conventional low-dose MHT administered in a combined, continuous regimen in postmenopausal women with migraine seeking treatment for menopausal symptoms [55]. Cyclical progesterone has been shown to worsen migraines in postmenopausal women [56]. For women with VMS and migraine, it is recommended to initiate at the lowest dose and increase gradually until the symptoms are controlled [48]. A recent case study demonstrated that lowering the dosage of transdermal estrogen can cause return of menstrual migraine attacks [57].

Recommendations and Key Messages

Alzheimer's Disease (AD)

- CEE+MPA increases the risk of all-cause dementia in women who initiate MHT at the age of 65 years or later, with the most common type of dementia being Alzheimer's disease (AD). ⊕⊕⊕◯ B
- ET is associated with a lower risk of dementia in premenopausal women who undergo oophorectomy, supporting the use of ET to prevent dementia in women with premature ovarian insufficiency (POI) and early menopause. ⊕⊕◯◯ C
- The current data do not recommend initiation of MHT for the primary prevention of AD in naturally menopausal women. ⊕⊕⊕◯ B

Parkinson's Disease (PD)

- ET should not be used for the prevention or treatment of PD in the majority of women who underwent menopause within the usual age range (45 years onwards). ⊕⊕◯◯ C
- For women who underwent premature (age <40 years) or early menopause (age 40 to <45 years), either spontaneous or iatrogenic, ET should be considered for the prevention of PD. ⊕⊕◯◯ C

Stroke

- The effect of MHT on stroke risk depends on the timing of initiation. ⊕⊕⊕⊕ A
- Women who initiate MHT <10 years after menopause onset or at ages <60 years are at similar risk of stroke compared to women who do not take MHT. ⊕⊕⊕⊕ A
- When initiated >10 years after menopause onset or among women >60 years of age, oral estrogen-containing MHT is associated with increased risk of stroke. ⊕⊕⊕⊕ A
- Stroke risk may vary by MHT administration route, dosage or formulation. ⊕⊕◯◯ C
- Transdermal administration routes and lower doses of MHT may be associated with a lower risk compared to oral and higher doses, respectively. ⊕⊕◯◯ C

Migraine

- For perimenopausal and postmenopausal women with migraine with aura, estrogen-containing oral contraceptives are associated with an increased risk for stroke and there may be an increased risk but of lesser magnitude with oral estrogen-containing HT. ⊕⊕⊕◯ B
- In perimenopausal women with migraine without aura, combined oral contraceptives (COC) given continuously, may be helpful in suppressing ovulation and preventing the triggering of menstrual migraines associated with estrogen withdrawal. Formulations containing estradiol or estetrol (E4) are considered safer due to more favorable thromboembolic profiles. However, COCs should be avoided in perimenopausal women with other vascular risk factors and should be stopped in women who develop migraine after initiation. ⊕◯◯◯ D

- In postmenopausal women with migraine, transdermal formulations of MHT are preferable to oral formulations, due to lower variability in estrogen levels. ⊕⊕◯◯ C
- For migraine, transdermal MHT formulations are preferable to oral formulations due to their more favorable thromboembolic profiles. ⊕⊕⊕◯ B
- In women with migraine with aura, non-hormonal interventions are effective alternative treatments for menopause-related VMS. ⊕⊕◯◯ C

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12. Breast Cancer

The incidence of breast cancer is rising globally, but rates vary across geographic areas. Therefore, currently available data may not be applicable everywhere.

Baseline Breast Cancer Risk

Whenever any relative risk of MHT is considered for a woman, it should be placed in the context of her personal breast cancer risk, which will vary according to a wide range of modifiable and non-modifiable risk factors [1]. The single most important non-modifiable risk factor is age and nearly a quarter of cases occurring in women over the age of 75.

Other non-modifiable risk factors to consider are strong family history of breast cancer, with or without being a carrier of a breast cancer susceptibility gene, a history of breast hyperplasia with atypia or lobular carcinoma in situ, and thoracic radiotherapy at a young age (usually after Hodgkin's disease). Reproductive history should also be considered, including early menarche, late menopause and late age at first full-term pregnancy. Breast density is associated with a higher risk of breast cancer in multiple observational studies, and MHT should be prescribed with caution [2].

Modifiable risk factors include weight, alcohol intake, smoking and levels of physical activity. There are limited data around diet as a risk for breast cancer, although this is confounded by the interplay of diet and body mass index (BMI). There are limited data suggesting that mastalgia could be associated with a higher risk of breast cancer. MHT-related mastalgia may be a sign of poor breast tolerance and may necessitate the adaptation of dose/type of treatment [3].

Evaluating and categorising baseline risk for breast cancer allows for an appropriate shared decision-making conversation with a woman considering MHT. Multiple and overlapping risks for breast cancer can be assessed using tools that resolve multiple inputs [4]. The Gail, IBIS and CanRisk tools are all freely available. The Australian IPREVENT combines available risk tools with a helpful interface to describe risk for women and their physicians [5]. A recommendation cannot be made to use a specific score [4].

MHT and Breast Cancer risk

The possible increased risk of breast cancer associated with MHT is small. Estimates vary according to regimen and a person's baseline risk. It is similar to or lower than the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption. The risk of alcohol consumption appears synergistic with MHT risk in current users based on the meta-analysis of epidemiological studies [6].

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 of the treatment. In all cases the absolute risk differences for an individual are small.

In the WHI trial for hysterectomised women, estrogen alone MHT (conjugated equine estrogens) was associated with a lower risk of breast cancer and lower breast cancer mortality. This association was strongest for women with fewer baseline risk factors for breast cancer and those who were MHT naive at baseline [7]. This reduction in risk has been seen in two subsequent meta-analyses, although in both

the WHI data are heavily weighted [8,9]. There is no difference between oral or transdermal estradiol and there is no robust evidence linking risk with dose of estrogen.

It is important to note that the majority of subjects in the WHI study were overweight or obese and treated with conjugated estrogens and not estradiol, which may have affected their basal breast cancer risk [10]. These outcomes cannot reliably be extrapolated to younger and less obese women and to estradiol. 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 may 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 [11,12].

Combined hormone therapy is associated with an increased risk of breast cancer that rises with duration and decreases progressively after treatment. Sequential regimens may pose lower risk than continuous ones. The WHI estrogen + progestogen trial and several large observational studies reported an increased risk after at least 5 years of use [7]. Only the unadjusted relative risk was significant, and when adjusted on risk factors, the significance was no longer reached [13]. The subtype of breast cancer associated with increased risk in these studies was predominantly Luminal A type (ER+ve PR+ve). No increase in HER2+ and triple negative subtypes has been reported [14]. Combined MHT can increase breast density, which may require additional radiological screening.

Data from the WHI study demonstrated no increased risk in first-time users of MHT during the 5–7 years since initiation of treatment [13].

Tibolone does not appear to be associated with an adverse effect on mammographic density or mastalgia. A trial of tibolone in breast cancer survivors was associated with a significant risk of breast cancer recurrence and increased breast cancer risk is seen both in meta-analysis and recent nested case control study [8,15]. Tibolone is not recommended for women with breast cancer or those with high risk of breast cancer [16].

Several studies suggest that micronized progesterone or dydrogesterone could be associated with a lower risk than synthetic progestogen. In particular, a large French 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 other synthetic progestogens [11]. A case–control study from France also showed a lower level of risk with progesterone than synthetic progestogens [17]. 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 [18]. Two UK nested case control studies saw a progressive increase in breast cancer risk with progestins with duration, and no increase at short term or a smaller increase with micronized progesterone or dydrogesterone at long term [15,19].

No increase in the rates of breast cancer or in breast density has been seen in observational studies of testosterone therapy in postmenopausal women [20] but there are insufficient data from randomized controlled trials (RCTs) to assess long term risk.

Currently available data imply no difference in risk between oral and transdermal routes of estradiol administration. 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 and dose of progestogens, and androgen administration.

The Levonorgestrel IUD (LNG-IUD) can be used during the menopausal transition. Meta-analysis of observational studies shows a small increased risk of breast cancer that rises with age. This risk estimate is confounded by prior use of hormonal contraception and potential bias of use towards women with higher risk of breast cancer [21]. The same studies show IUD was associated with fewer endometrial, cervical and ovarian cancers. As with oral progestogens, LNG-IUD is not recommended in women at high baseline risk of breast cancer.

Observational data do not suggest any increased breast cancer risk from vaginal delivery of hormones in women with no history of breast cancer [8].

Treatment after breast cancer

Mortality rates for breast cancer are falling, which relates to improvements in awareness, early detection and therapies. Most breast cancers (80%) express the estrogen receptor, and therapies include ovarian function suppression, SERMs (tamoxifen) and aromatase inhibitors; all of which can provoke or exacerbate symptoms of the menopause. Management of menopausal symptoms for women with breast cancer is an important survivorship issue that affects quality of life and may impact recurrence and survival rates due to poor adherence with prescribed endocrine therapies [22-24]. Failure to address menopausal symptoms can lead to poor endocrine therapy adherence and compromise best oncological care. Thus, people affected by breast cancer should be offered routine proactive enquiry about menopausal symptoms and these should be adequately addressed.

There is no evidence that non-hormonal therapies used for the treatment of vasomotor symptoms (VMS) after breast cancer affect breast cancer recurrence rates or mortality, and these should be offered as first line treatment [23-25]. An RCT in women with ER+ breast cancer reported that a neurokinin (NK)‑1 and NK-3 receptors antagonist, elinzanetant, was able to treat the VMS, improve sleep, and quality of life, during the endocrine treatment for breast cancer for 1 year [26]. Long-term safety is still lacking.

Genito-urinary symptoms associated with the menopause are a common problem for women after breast cancer and more common in women who were prescribed aromatase inhibitor therapy. Trials show no evidence that non-hormonal treatments for genitourinary syndrome of menopause (GSM) affect breast cancer recurrence rates or mortality. Vaginal estrogen therapy is associated with minimal rises in serum estradiol/estriol levels that vary according to estrogen preparation, but do not go above the normal post-menopausal range. Large observational studies have shown no increase in breast cancer mortality with use of vaginal estrogens after breast cancer [25]. A Danish study in women treated for breast cancer between 1997 -2004 reported a rise in breast cancer recurrence rates in women using the relatively high dose vaginal estrogens prescribed at the time [27]. Vaginal estrogens should be used at lowest effective dose in women using Aromatase Inhibitors (AIs) after careful counselling. Use of vaginal estrogen in women prescribed tamoxifen appears safe.

There are no randomized data of contemporary MHT after breast cancer with current standard of care breast treatments. A meta-analysis of RCTs and observational studies has shown no increase in recurrence risk although the tibolone study and one other RCT, which was terminated early, demonstrate a rise in recurrence rates [16,28,29]. After ER negative cancer it is biologically less plausible

that MHT would increase recurrence rates but there are no data to reassure that MHT is safe and there are concerns that MHT could promote either a ER+ recurrence or a second cancer. The effect of contemporary MHT formulations in people treated with current standard of care breast cancer therapies has not been studied and is an ongoing research question.

Recommendations and Key Messages

- In considering breast cancer risk when prescribing MHT it is important to assess the baseline risk. GPP
- Breast cancer risk with MHT varies according to the regimen and the individual's baseline risk. Scores are available to help evaluate the baseline risk. The Gail https://bcrisktool.cancer.gov/, IBIS https://ibis.ikonopedia.com/ and CanRisk https://www.canrisk.org/ tools are all freely available. A recommendation cannot be made to use a specific score. ⊕⊕⊕◯ B
- Breast cancer risk observed with MHT may be partially decreased by selecting women with a lower baseline risk, including low breast density, and by providing education about preventive lifestyle measures (reducing body weight, alcohol intake and increasing physical activity). ⊕⊕⊕◯ A
- Increased breast density is associated with a higher risk of breast cancer and MHT should be prescribed with caution. ⊕⊕⊕◯ B
- Careful radiological surveillance should be considered in cases of high breast density in women using MHT. Combined (estrogen-progestogen) MHT can increase breast density, which may require additional radiological surveillance. ⊕⊕⊕◯ B
- The risk of breast cancer attributable to MHT is small and is similar to, or lower than, the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption. ⊕⊕⊕⊕ A
- Combined MHT is associated with an increased risk of breast cancer that increases with duration and decreases progressively after treatment. ⊕⊕⊕⊕ A
- Sequential combined regimens may pose lower risk than continuous combined regimens. ⊕⊕⊕◯ B
- Estrogen-alone MHT is associated with a lower risk of breast cancer than that with combined MHT regimens. ⊕⊕⊕◯ B
- There is no difference in risk between oral or transdermal estradiol. There is no robust evidence linking risk with dose. ⊕⊕◯◯ C
- The increased risk of breast cancer is primarily associated with the addition of a synthetic progestogen to estrogen therapy (e.g. CEE + MPA continuous combined therapy) and related to the duration of use. ⊕⊕⊕⊕ A
- The risk appears lower with micronized progesterone, or with dydrogesterone than with another synthetic progestogen, and this may be associated with a better risk profile for breast cancer than with other synthetic progestogens. ⊕⊕⊕◯ B

- There are not enough data to fully evaluate possible differences in the incidence of breast cancer using different types, doses and routes of progestogens and androgen administration. ⊕⊕◯◯ C
- Data do not suggest any increased breast cancer risk from vaginal delivery of hormones in women with no history of breast cancer. ⊕⊕◯◯ B
- The levonorgestrel intrauterine device is not recommended in women at high baseline risk of breast cancer. ⊕⊕⊕◯ B
- MHT, including tibolone, is not recommended for women with breast cancer or for those at high risk of breast cancer. ⊕⊕⊕⊕ A
- No increase in the rates of breast cancer or in breast density has been observed with testosterone therapy in postmenopausal women. There are insufficient data from RCTs to assess long-term risk. ⊕⊕◯◯ C
- If mastalgia develops on MHT, it may be a sign of poor breast tolerance and necessitate the adaptation of dose/type of treatment. ⊕⊕◯◯ C
- Proactive management of menopausal symptoms in breast cancer survivors improves quality of life and medication adherence. ⊕⊕⊕◯ A
- Individuals affected by breast cancer should be offered routine proactive enquiry about menopausal symptoms and these should be addressed. GPP
- There is no evidence that non-hormonal therapies used for the treatment of VMS after breast cancer affect breast cancer recurrence rates or mortality, and these can be offered as first-line treatment. ⊕⊕⊕⊕ A
- Trials show no evidence that non-hormonal treatments for GSM affect breast cancer recurrence rates or mortality. ⊕⊕⊕◯ A
- Vaginal estrogen therapy is effective for GSM in breast cancer survivors and appears safe in women on Tamoxifen. ⊕⊕⊕◯ B
- In women on aromatase inhibitors who have not responded to non-hormonal treatments, individualized treatment options should be discussed with a breast cancer specialist. ⊕⊕◯◯ C
- There is a lack of safety data supporting the use of MHT (estrogen therapy or estrogen–progestogen therapy) in breast cancer survivors. ⊕⊕⊕◯ B

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13. Endometrial Safety & Bleeding

Unscheduled bleeding on menopausal hormone therapy (MHT) is defined as any bleeding which occurs after initiating or changing a continuous combined MHT preparation, or bleeding which occurs in addition to the scheduled monthly withdrawal bleed, in women taking cyclical or sequential MHT preparations [1,2]. Unscheduled bleeding within the first six months of initiating MHT or, within three months of a change in dose or preparation, in those already established on MHT, is very common. Up to 38% of people using sequential MHT and 41% using continuous combined MHT report unscheduled bleeding [3]. Consequently, it is a significant indicator for a consultation repetition and cessation of MHT [4].

The two principal concerns with unscheduled bleeding are what this may represent and how it can be controlled. Overall, the incidence of endometrial cancer in women on MHT is low but this will vary depending on their background risk of endometrial cancer [2]. Endometrial cancer is one of the commonest female cancers globally. The incidence increases with age, and the incidence is increasing, particularly in the western world [5]. Three to ten percent of women not on MHT, who present with postmenopausal bleeding (PMB), are diagnosed with endometrial cancer [6,7]. A BMI ≥40 confers a tenfold higher risk when compared to a BMI within the normal range [8] and hereditary conditions such as Lynch or Cowden syndrome can increase risk by 30-50%. Minor risk factors include BMI 30-39, diabetes and a history of polycystic ovarian syndrome. Unopposed estrogen increases the risk of endometrial hyperplasia and endometrial cancer [9] and progestogens should be added cyclically in a sequential fashion/order, or continuously to MHT to minimise this risk. The type and dose of both the estrogen and progestogen will influence the risk of endometrial cancer in a duration dependant manner. More than six months of unopposed estrogen or 12 months of tricycling (estrogen daily with a progestogen course every 3 months) are considered major risk factors for endometrial cancer [2,9,10]. Administration of daily (continuous) progestogen suppresses endometrial growth, leading to amenorrhoea and endometrial atrophy [11]. This reduces the risk of endometrial cancer, compared with non-users, with the greatest effect seen in women with a BMI ≥ 30 [12-14]. In women without unscheduled bleeding, the risk of endometrial cancer with standard preparations is <1% [15]. Medroxyprogesterone acetate (MPA) or norethisterone (NET) administered for 10-12 days each 28-day cycle are not associated with an increased risk of endometrial cancer compared to non-users. However, less than 10 days per 28-day cycle for 6 months or more is associated with a threefold higher risk (RR 3.1, 95% CI 1.7-5.7) [15,16,17]. Micronized progesterone (MP), in conjunction with standard dose estrogen, provides endometrial protection if given at a dose of 200mg for 12-14 days per month, for up to five years use [18]. If MTH is used sequentially for more than five years, the endometrial cancer risk increases almost threefold (RR 2.9 (95% CI 1.8-4.6)) [15-18]. “Off label” use of vaginal micronized progesterone at similar doses to oral micronized progesterone appears to provide endometrial protection for 3 years but there are insufficient data on endometrial protection when used at lower doses or for more than three years [18-20]. The 52-mg LNG IUD offers endometrial protection against ultra-low to high dose estrogen for up to five years of use in both peri- and postmenopausal women [21-24]. It is not known whether a malpositioned 52-mg LNG IUD provides adequate endometrial protection when used as part of MHT. If the IUD is > 2 cm from the fundus, or within the cervical canal (fully or partially) or there are relevant symptoms (e.g. pain or bleeding) then it is suggested that the IUD is removed and replaced [21].

Significance of unscheduled bleeding on MHT

Unscheduled bleeding is any bleeding outside of the normal bleeding pattern expected for the MHT preparation being used. Sequential MHT is usually prescribed for peri-menopausal women. Estrogen is used daily with a progestogen added for 10-14 days of the cycle. 90% of women on this combination preparation will have a cyclical bleed (usually at the end of the progestogen phase), lasting 3-7 days which is generally lighter than premenopausal menstruation. Prolonged or heavy withdrawal bleeding is not normal, nor is persistent (almost daily) bleeding. Continuous combined MHT is usually prescribed for post-menopausal women who have had amenorrhoea for at least 12 months before starting MHT. Women should not bleed after the first six months on this combination [15,19]. Unscheduled bleeding within the first six months of starting any type of MHT occurs in up to 40% of women [2,25]. Once established, continuous combined preparations are associated with less unscheduled bleeding than sequential regimens in postmenopausal women [15,26-28], but in perimenopausal women, endogenous follicular activity may result in irregular bleeding.

There are limited data on the rates of endometrial hyperplasia and cancer in women who present with unscheduled bleeding on MHT [2]. Most studies of sequential and combined MHT suggest that the majority of women who present with unscheduled bleeding and a thickened endometrium (> 5mm) will have a normal endometrial biopsy [1,29-33] and up to 30% will have an endometrial polyp [34]. Endometrial hyperplasia and cancer risk in MHT users with standard dose of estrogen appears lower than that in non-users with PMB, but it may increase with duration of use, and the risk is higher for sequential MHT rather than continuous MHT. This may reflect the dose and duration of progestogen per month [2].

Investigation of Unscheduled bleeding on MHT

Following clinical assessment and examination a transvaginal ultrasound (TVS) is the initial investigation of choice and the measurement of endometrial thickness and is used as a tool to exclude endometrial pathology. Ultrasound provides high diagnostic accuracy as a first line investigation for women who present with PMB [35-39]and is generally more acceptable to women than hysteroscopy or biopsy [40,41]. TVS is more accurate than transabdominal ultrasound (TAS) with double-layer endometrial thickness measured at the point of its maximal width [36]. However, the endometrial thickness must be clearly seen from cervix to fundus to utilize this tool. If it is obscured by leiomyomas, adenomyosis, marked obesity or axial uterus, alternative means should be employed. Evidence in relation to the sensitivity of TVS in predicting cancer risk in women with unscheduled bleeding on MHT is scarce, as large studies assessing this in women with PMB often exclude MHT users or do not provide subgroup analyses of MHT preparation or dose [2]. Based on a 26% (95% CI 25-27%) prevalence (pre-test) probability of endometrial disease (carcinoma and hyperplasia) in women with PMB, the post-test probability after a negative scan is reduced to 2.4% (95% CI 1.3–3.9%) when an endometrial thickness value of ≤4 mm is used and 5.0% (95% CI 2.9–9.1%) when the value ≤ 5 mm is used [37]. Whilst the >5 mm cut off would reduce the number of cases requiring further invasive investigations, it would also reduce the sensitivity and negative predictive value of TVS endometrial thickness for endometrial cancer detection in all women [42-44]. For women on continuous combined therapy the same cut off value, i.e. <4mm, is recommended as for postmenopausal bleeding [2]. For sequential MHT there is a paucity of data. Endometrial thickness varies within the natural menstrual cycle and the same is likely with sequential preparations. An endometrial thickness of <7 mm has a 99% negative predictive value for endometrial cancer with standard dosing of micronized progesterone MPA, regardless of the time

of the cycle [45,46]. The acceptable upper endometrial thickness limit is not known but, in the absence of reassuring data for any higher cut off, >7mm is recommended [2].

Blind outpatient endometrial biopsy, in comparison to hysteroscopy, is cost-effective and quicker to achieve [47]. However, the failure rate of a blind endometrial biopsy in postmenopausal women is 12%, and inadequate rates are 22%. In women taking MHT these proportions may be lower owing to reduced rates of atrophic changes. Hysteroscopy is more invasive and resource heavy than blind endometrial sampling but has a lower failure rate (3.4%) in postmenopausal women [6]. The post-test cancer probability is 71.8% after a positive result and 0.6% with a negative result; sensitivity is 86.4% and specificity - 99.2% [6]. Removing focal lesions like polyps, as part of a 'see-and-treat' procedure, may improve patient experience by reducing the total number of appointments and procedures. One RCT reported that 50% of women included with PMB and a TVS endometrial thickness ≥ 4 mm with a negative blind endometrial biopsy, had an underlying endometrial polyp, of which 6% contained endometrial atypical endometrial hyperplasia or endometrial cancer [34]. Women who have a normal hysteroscopy and biopsy can be reassured for six months after this outcome even if unscheduled bleeding continues [2].

Adjusting MHT to reduce unscheduled bleeding episodes

Although unscheduled bleeding on MHT is common, there are few studies reporting on interventions that reduce recurrent episodes. The suggestions outlined in these recommendations are based on the available evidence and clinical experience [2] (Recommendations for managing unscheduled bleeding on HRT). The general principles are: to optimize any medical co-morbidities, such high as BMI, that may impact on the endometrial response; to ensure compliance with all aspects of MHT; to ensure an adequate progestogen is used at the appropriate dose and for the appropriate length of time. Further adjustments maybe necessary including change in the type and/or dose of either the estrogen or the progestogen component [2]. Synthetic progestogens containing NET, MPA or levonorgestrel are associated with higher rates of cumulative amenorrhoea, when compared to micronized progesterone as they are less rapidly metabolised and provide high oral bioavailability [47,48]. Switching from transdermal to oral therapy may also reduce bleeding events; in women taking continuous combined MHT, oral preparations were associated with higher rates of amenorrhoea compared to transdermal preparations at 3 months (65-91% vs 40-65%) and over 12 months cumulative amenorrhoea was lower with transdermal therapy compared to oral (9-27% vs 18-61%) [49]. The 52-mg LNG-IUD, which is available in many countries, is associated with good endometrial suppression and high amenorrhea rates. Non-proliferative endometrium is reported on histology in 89.5% at 12 months, increasing to 94.8% at two years and 97.5% at five years [50,51]. In postmenopausal women taking standard dose estrogen, 52-mg LNG-IUD has a reported amenorrhoea rate at 12 months of 80% compared with 67% for daily oral micronized progesterone [52].

Other options that can be considered are: tibolone which achieves high amenorrhea rates with good endometrial safety, [53,54] or Duavive which is a combination of a SERM (bazodoxifene) and conjugated equine estrogens and associated with high amenorrhea rates [55]. Alternatively in women < 50 years who are at low risk of thrombosis, a combined oral contraceptive containing estradiol may be effective [56]. Finally, if bleeding is persistent, consider reducing or stopping the MHT and offer non-hormonal alternatives.

Recommendations and Key Messages

- Optimization of modifiable factors such as BMI and diabetes can reduce episodes of unscheduled bleeding on MHT and endometrial cancer risk. ⊕⊕⊕◯ A
- Ensure compliance with the prescribed medication with particular attention to the timing of pill/gel/patch/spray application and the timing/duration of progestogen. GPP
- A monthly progestogen (sequential or continuous), in a dose proportionate to the estrogen dose, is recommended in women with a uterus. ⊕⊕⊕⊕ A
- Women using sequential MHT should have a minimum of 10 days NET or MPA, or 12 days of dydrogesterone or micronized progesterone per 28-day cycle. ⊕⊕⊕⊕ A
- Women taking cyclical progestogen for less than the recommended time/month should be advised that they have an increased risk of endometrial hyperplasia and cancer which increases with dose and duration of treatment. ⊕⊕⊕◯ B
- Women taking appropriately dosed sequential micronized progesterone should be advised that this does not appear to increase endometrial cancer risk but there is limited evidence for its use beyond 5 years. ⊕⊕⊕◯ B
- Amenorrhoeic postmenopausal women taking a continuous combined MHT preparation (standard dose) should be aware that they have a lower endometrial cancer risk than non-MHT users. ⊕⊕⊕⊕ A
- Women taking a sequential MHT over the age of 45 years should be offered a change to continuous combined MHT after five years or by age 54 years, whichever comes first. ⊕⊕⊕◯ B
- Women taking high-dose estrogens should be informed that there are limited data relating to the optimal progestogen dose needed to provide endometrial protection. Higher doses of progestogen in proportion to the dose of estrogen are recommended. ⊕⊕◯◯ B
- The 52-mg LNG IUD offers endometrial protection against ultra-low to high-dose estrogen for up to 5 years of use in both perimenopausal and postmenopausal women. ⊕⊕⊕⊕ A
- Women with a malpositioned 52-mg LNG IUD should be aware that it is uncertain whether this provides adequate endometrial protection when used as part of MHT. If the IUD is >2cm from the fundus, or within the cervical canal (fully or partially) or there are relevant symptoms (e.g. pain or bleeding), then it is suggested that the IUD is removed and replaced. ⊕◯◯◯ C
- Women presenting with unscheduled bleeding on MHT should be assessed for their individual risk factors for endometrial cancer, their bleeding pattern and the type and dose of MHT preparation they are taking. GPP
- Pelvic and abdominal examinations should be performed where applicable and initial investigations should be considered, including cervical cytological screening, a lower genital tract infection screen and a pelvic ultrasound. GPP

- In the absence of risk factors for endometrial cancer, the overall risk of endometrial cancer is likely to be lower than those of a similar age not on MHT, so adjustments in the progestogen dose or type may be considered before further investigation. ⊕⊕◯◯ A
- If unscheduled bleeding continues after 6 months of MHT usage, investigation and further adjustments/change to the progestogen regimen are needed. ⊕⊕⊕◯ A
- If there is one major or two minor risk factors for endometrial cancer, then further investigations should be performed immediately. ⊕⊕⊕⊕ A
- The initial investigation should be a transvaginal ultrasound. The priority for these investigations will include multiple factors, including the presence of risk factors for endometrial cancer, the type of MHT preparation, the type of bleeding and local resources. ⊕⊕⊕◯ A
- On continuous combined MHT, an endometrial thickness >4mm is considered abnormal. ⊕⊕⊕⊕ A
- On sequential combined MHT, the endometrial thickness can vary throughout the cycle. Ideally, the ultrasound should be timed just after the withdrawal bleed and any measurement >7mm should warrant further investigation. An increased endometrial thickness outside this timeframe should prompt a re-scan at the appropriate time. ⊕⊕◯◯ B
- Women with an endometrial thickness within normal parameters should be reassured and offered adjustments to their MHT. If bleeding persists beyond 6 months despite a normal result, then endometrial assessment is recommended. ⊕⊕◯◯ A
- When the endometrial thickness is abnormal, or if the endometrial thickness cannot be adequately visualized, further endometrial assessment is recommended. ⊕⊕⊕◯ A
- In the absence of significant risk factors for endometrial cancer, there is no need to stop the MHT before investigation and suitable adjustments to the progestogen can be made during this time. ⊕⊕◯◯ B
- Endometrial assessment can either be performed by a blind outpatient endometrial biopsy or hysteroscopy with endometrial sampling, if acceptable to the woman and within clinic resources. ⊕⊕◯◯ B
- If unscheduled bleeding persists 3 months after a negative blind biopsy, then hysteroscopic assessment is advised. ⊕⊕◯◯ B
- In the presence of an insufficient sample on blind biopsy, hysteroscopy should be considered. ⊕◯◯◯ B
- If proliferative endometrium is reported on blind biopsy in women on continuous combined MHT and there are risk factors for endometrial cancer, then hysteroscopy is advised. ⊕⊕◯◯ B

- If hyperplasia with atypia or endometrial cancer is reported, advise weaning off MHT, discuss non-hormonal alternatives and refer urgently to a relevant specialist for further management. ⊕⊕⊕◯ A
- If unscheduled bleeding persists for more than 6 months after a previous negative hysteroscopy, consider repeat investigations. ⊕◯◯◯ B
- Consider switching women with ongoing unscheduled bleeding on continuous combined MHT back to sequential MHT, particularly if they are still in perimenopausal age. ⊕◯◯◯ B
- Consider lowering the estrogen dose, as lower doses are associated with higher rates of amenorrhea. ⊕◯◯◯ B
- Consider increasing the dose and duration (with sequential therapy) of the progestogen. ⊕◯◯◯ B
- Consider switching from micronized progesterone to oral NETA or MPA as these have higher rates of amenorrhea than micronized progesterone. ⊕⊕◯◯ B
- If it is clinically safe to do so, consider switching to an oral preparation as oral MHT may achieve greater cumulative rates of amenorrhoea than transdermal MHT. ⊕◯◯◯ B
- Consider the 52-mg LNG IUD as an option (if available), particularly in women who have endometrial cancer risk factors. ⊕⊕◯◯ B
- Alternative options include CEE with bazedoxifene or tibolone where available. If the woman is aged under 50 years and has no risk factors for thrombosis, an estradiol-containing combined oral contraceptive preparation can be considered. KM
- If bleeding is persistent, consider reducing or stopping the MHT and offer non-hormonal alternatives. GPP

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14. Ovarian Cancer

The IMS 2016 Recommendations stated that "Based on the evidence to date the association between MHT use and ovarian cancer remains unclear". The 2024 revision of the NICE Menopause guidelines [1] included a review of 18 studies (1 RCT and 17 observational studies, 4 of which had been published since 2016). This review concluded that although the evidence from the Women's Health Initiative suggested there was no significant increase in ovarian cancer cases in people taking MHT compared to those not taking HRT, the total number of ovarian cancer cases in both arms was very small, making the evidence less robust [1-19].

Evidence from observational studies confirmed a small but measurable increased risk of ovarian cancer in people taking MHT. The sample sizes and number of ovarian cancer diagnoses were much larger in the observational studies than the RCTs, which led the NICE committee to conclude that these findings were more robust. NICE concluded that overall, the absolute risk was small, given the low baseline risk of ovarian cancer, and they estimated that MHT use (irrespective of type {EP or E}, or route of administration) increases the risk of ovarian cancer incidence by approximately 1 per 1000. They recommend that this be explained when MHT is being considered or initiated. No recommendation was made on ovarian cancer mortality due to insufficient data. The analysis was unable to address the issue of the impact of duration for combined MHT use, however NICE did note that the increased risk associated with estrogen only MHT was restricted to those using it for longer than 5 years. NICE specifically highlighted a lack of evidence in minority ethnic groups and non-binary people registered female at birth who have taken cross hormones in the past, which should be the focus of further research going forward [1]. These findings are generally in agreement with the North American Menopause Society [20] and outline a very small increased risk of ovarian cancer associated with MHT, however, for most women the benefits of treatment are likely to outweigh the risks outlined above.

As a result of advances in surgical care and maintenance therapies (particularly Poly (ADP-ribose) polymerase (PARP) inhibitors) the survival times for ovarian cancer are increasing. A Cochrane review that included three historical RCTs involving 350 women reported between 1999 and 2015 found uncertain evidence for efficacy or safety of MHT in women diagnosed with ovarian cancer [21]. MHT can be used in high grade serous, mucinous, clear cell and endometrioid cancers and borderline tumours [22-26], but should be avoided in low grade serous, granulosa cell and sex cord stromal tumours [22,23,27]. A prospective cohort study of women diagnosed between 2012 and 2015 (n=690) in Australia demonstrated that the pre-diagnosis MHT use was associated with improved ovarian cancer specific survival in the most common histological subtype high grade serous ovarian cancer (HGSOC) (n=525) (HR = 0.69, 95%CI 0.54–0.87) [28]. However, this did not translate into a survival benefit when MHT was commenced in women with HGSOC who were pre-/perimenopausal or aged ≤55 years at the time of diagnosis (n = 259) (HR = 1.04, 95%CI 0.48–2.22) [28]. It should be noted that none of these studies were performed before the maintenance treatments such as bevacizumab and PARP inhibitors were approved and there are no data to support or refute the use of MHT in combination with these medications.

Recommendations and Key Messages

- In individuals with ovaries, there is a very slight increase in ovarian cancer risk with combined MHT. ⊕⊕⊕⊕ A
- In individuals with ovaries, there is a very slight increase in ovarian cancer risk with estrogen-only MHT taken for 5 years or more. ⊕⊕⊕⊕ A
- Pre-diagnosis use of MHT does not appear to have a detrimental impact on ovarian cancer outcomes. ⊕⊕⊕◯ B
- MHT is not usually contraindicated following treatment for epithelial ovarian cancer, and potential risks and benefits should be discussed with women. ⊕⊕⊕◯ A
- Although the majority of high-grade serous and endometrioid ovarian cancers express the estrogen receptor, the limited RCT data do not suggest an increased risk of disease recurrence with systemic MHT. It may be appropriate to offer non-hormonal options in the first instance, particularly for women who do not have the health impacts of a premature or early menopause. ⊕⊕⊕◯ B

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15. Lung Cancer

Lung cancer incidence ranks second in the list of female cancers but surpasses breast cancer as the leading cause of cancer death among females in more developed countries [1,2]. A relationship between menopause hormone therapy (MHT) and lung cancer is biologically plausible because estrogen receptors (α and β) are present in both healthy lung tissue and lung cancers. This may be linked to survival outcomes, with ER β expression associated with improved prognosis in non-small cell lung cancer (NSCLC) [3]. Advanced age and smoking are the main risk factors and are the key confounding variables in studies linking MHT to lung cancer risk.

Link of MHT / menopause to lung cancer incidence

There has been considerable debate about the possible relationship of menopause and MHT to lung cancer risk. 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 [4].

However, a recent large registry study found that reproductive factors such as age at menopause and menopause status were not associated with the incidence of lung cancer and its subtypes [5].

In a population-based cohort study, women who had undergone premenopausal bilateral oophorectomy (n=1562) were compared to a random sample of age matched, non-oophorectomized women (n=1610). It was found that there was no difference in the incidence of lung cancer between the groups after a median follow up of 18 years. Use of estrogen therapy through the age of 50 years in this population did not modify the results [6].

Link of MHT / menopause to lung cancer mortality

In terms of mortality, the findings from various studies have been contradictory. In the Women's Health Initiative (WHI) trials, the incidence of lung cancer was similar in MHT users and non-users; Hazard Ratio (HR) was 1.17, 95% CI 0.81–1.69 in the estrogen-alone arm (E) and HR 1.23, 95% CI 0.92–1.63 in the estrogen/progestogen (E+P) group. However, 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) [7,8].

After 14 years cumulative follow up in the WHI trials, there were 219 lung cancer cases in the E + P group and 184 in the placebo group (HR 1.12 95% CI 0.92-1.37). Whilst there were more deaths in the E +P group, the difference was not statistically significant, and the increase in deaths from lung cancer during intervention in the E + P women was attenuated after discontinuation of MHT [9].

A large Cochrane review of 22 studies involving 43,637 (including many women from the WHI studies) also found that long term continuous combined MHT increased lung cancer death (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000) [10].

Around the time of the WHI report and the Cochrane review, the United States Preventive Services Task Force concluded that MHT (E /E+P) had no significant effect on lung cancer risk. The data, rated as low to moderate quality, included dual review of abstracts, full-text articles, and meta-analyses with at least 3 similar studies available [11].

In contrast to WHI, a large cohort study of UK biobank postmenopausal participants did not demonstrate significant "cause specific" lung cancer mortality association between MHT users compared to non-users in women with natural and surgical menopause [12].

Also, contrary to the WHI findings, a systematic review and meta-analysis of 11 studies of MHT and lung cancer mortality found that the pooled HR of MHT in relation to lung cancer mortality was 0.97 (95% CI 0.83-1.12, p=0.006) in all studies, and 0.80 (95% CI 0.69-0.92, p=0.278) in prospective cohort studies. The authors concluded that there was a possible protective role of MHT for lung cancer mortality in the pooled prospective cohorts, but not in the pooled retrospective cohorts and post hoc analyses of randomized trials. The results were regarded by the authors as being robust, but it was recommended that further studies should be conducted that better control for variables such as smoking, type and timing of MHT and menopausal status [13].

Link of MHT to lung cancer survival

Lung cancer survival was examined in a retrospective review and meta-analysis. The study analyzed 1054 female lung cancer cases with MHT and 1528 lung cancer cases without MHT. Meta-analysis showed that compared with patients without MHT, patients using MHT had an increased survival time of 5 years (Effect Size=0.346; 95% CI 0.216 to 0.476; P<0.001) [14].

The 2022 hormone therapy position statement of The Menopause Society pointed out that a number of observational studies, including meta-analyses, were conflicting in their findings and showed no consistent link between MHT and lung cancer risk [15].

Type, timing and duration of MHT

Some publications have analyzed the type, timing and duration of MHT usage and lung cancer risk in greater detail. The overall message appears to be that risks do not seem to substantially increase among women with longer duration of MHT.

An older meta-analysis of 18 various types of studies (RCTs, case–control studies, cohorts, cancer registries) showed an overall benefit for ever use of MHT (RR 0.80, 95% CI 0.72–0.89). However, the reduction in risk was seen in E-only users, whereas there was no significant effect associated with E+P use. The authors noted that significant differences were found in analyses only when smokers and non-smokers, various hormone regimens, or histological subtypes were pooled [16].

A large systematic review and meta-analysis of different types of MHT usage and lung cancer risk was recently reported. A total of 22 studies (13 prospective cohorts and 9 case controls), comprising of 911,194 participants and 17,329 lung cancer cases, were included. Compared to never users of MHT, current users were found to have a lower incidence of lung cancer in the pooled cohort studies (RR 0.91 95% CI 0.86-0.97) and ever users of MHT had a lower incidence of lung cancer (OR 0.75 95% CI 0.69-0.81). It was emphasized that the roles of hormone receptor status and single nucleotide polymorphisms should be taken into account when individualizing MHT [17].

In a recent 16-year nationwide population based matched cohort study, 38,104 postmenopausal women who were treated with MHT were compared to 152,416 matched participants not treated with MHT. After adjustment for variables there was no association found between MHT and lung cancer development (HR 0.886 (95% CI 0.666-1.305 P = 0.443)). However, sub-analysis detected that higher dosage and longer-term use of MHT was associated with a reduced risk of lung cancer [18].

Other studies of timing and duration of MHT have also shown a reduction in risk of lung cancer with MHT. Data from the multicenter randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (1993-2001) were published in 2020 [19,20]. Women aged 50-74 years were followed prospectively for up to 13 years for cancer screening. In the cohort of 75,587 women, 1147 women developed non-small cell lung cancer (NSCLC) after median follow-up of 11.5 years. Half the cohort were current MHT users, 17.0% former users, and 33.6% never users. On multivariable analysis, current MHT use was associated with reduced risk of NSCLC compared with never users (HR 0.80; 95% CI 0.70-0.93; P = 0.009) [20].

In women with history of endometriosis, E alone significantly reduced the risks of lung cancer (p=0.011) whereas combined MHT had no significant effect [21]. However, it should be noted that women with a history of endometriosis are commonly advised to use combined MHT, even after hysterectomy.

Finally, a recent narrative review concluded that neither MHT nor oral contraception are consistently associated with significant differences in all-cause mortality or disease-specific lung cancer mortality [22].

Recommendations and Key Messages

- Although estrogen receptors are present in healthy and cancerous lung tissue, recent studies do not confirm a firm link between natural and surgical menopause status and risk of lung cancer. KM
- Data on MHT and lung cancer are inconsistent with no clear effect of MHT on lung cancer incidence or mortality. KM
- HCPs should be advised that the role of menopause and MHT on lung cancer incidence and mortality remains inconclusive. ⊕⊕⊕◯ B
- Whilst HCPs should consider the risk of lung cancer when advising women about MHT, it should not be a reason to avoid prescribing if there are no other risks or contraindications. ⊕⊕⊕◯ A
- When counselling women about risk factors for lung cancer, it is important to emphasize the key modifiable risks such as smoking. GPP
- HCPs should be informed that it remains unclear what the optimal MHT regimen and duration is to minimize lung cancer risks, and more research is required to confirm this. ⊕⊕◯◯ B
- Women diagnosed with lung cancer who are deriving benefit from their MHT may not need to discontinue it, as there does not appear to be an adverse effect on survival times, and there may even be a beneficial effect. ⊕⊕⊕◯ B

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16. Colorectal Cancer

Colorectal cancer (CRC) ranks third in global cancer prevalence [1]. Age-standardized incidence rates are lower in women [2]. Observational studies have identified an association between higher endogenous estradiol levels and a reduced CRC risk in postmenopausal women [3], whereas hormone deprivation, whether through unilateral or bilateral oophorectomy, has been linked to an increased CRC risk, as demonstrated in two systematic reviews and meta-analyses [4,5]. However, findings are not entirely consistent, as evidenced by the divergent results of two subsequently published large-scale prospective observational studies [6,7].

An umbrella review concluded that hormone therapy (HT) was associated with a reduced incidence of CRC in both randomized controlled trials (RCTs) and observational studies, although the authors assessed the overall quality of the evidence as moderate to low [8]. More recent observational studies have likewise reported a decreased CRC risk associated with menopausal HT [9]; however, these findings have not been consistently replicated by other investigators [10]. The most robust evidence originates from the combined arm of the Women's Health Initiative (WHI) study, a placebo-controlled RCT involving 16,608 participants. In this trial, women receiving CEE+MPA experienced a 44% reduction in CRC incidence compared to those given a placebo [11]. Conversely, no significant difference was observed between treatment and placebo in the estrogen-only arm [12]. Moreover, the apparent protective effect of combined hormone therapy was partially confounded by the more advanced stage of the tumors detected in the treatment group. Furthermore, the reduction in CRC incidence observed at the end of the 5.6-year study period was no longer evident after 24 years of follow-up [13].

Biochemical studies provide mechanistic support for these clinical observations. The normal colonic epithelium exhibits differential expression of the two main isoforms of estrogen receptors (ER), with ERβ being predominant over ERα. In malignant epithelium, this pattern is reversed, suggesting a potential protective role for ERβ against CRC [14]. Consistently, ERβ expression has been associated with favorable prognostic features, including reduced CRC-specific mortality, across various tumor series [15-17]. Preclinical and molecular research is increasingly elucidating both genomic and non-genomic pathways through which estrogens may exert their effects [18]. Genome-wide analyses have also identified genetic variants that may influence the impact of menopausal HT on CRC risk, potentially explaining the heterogeneity of findings in clinical studies [19]. Moreover, a polygenic risk score has been proposed to identify women who may derive greater protective benefit from HT in the context of CRC risk reduction [20].

Recommendations and Key Messages

- Given its high global prevalence as the third most commonly diagnosed malignancy, colorectal cancer (CRC) requires the implementation of effective risk mitigation strategies. GPP
- Consistent findings from epidemiological studies indicate a lower incidence of CRC in women relative to men. ⊕⊕⊕◯ B
- The lower incidence of CRC in women relative to men may reflect a protective effect of estrogen. KM
- While several studies have reported an inverse association between endogenous estrogen levels and CRC risk, the evidence remains inconclusive. ⊕⊕⊕◯ B
- A protective role of MHT has been supported by findings from the combined estrogen-progestin arm of the WHI trial and corroborated by a comprehensive umbrella review; however, the observed protective effect attenuated over time, and no significant reduction in CRC-specific mortality was observed. ⊕⊕⊕◯ B
- Inter-individual variability in genetic determinants of estrogen signaling may account for differential responsiveness to estrogen-mediated protection, potentially influencing observed heterogeneity in CRC outcomes. ⊕⊕◯◯ C
- Despite suggestive evidence, HT is not currently endorsed as a viable strategy for CRC risk reduction. ⊕⊕⊕◯ B
- Current public health guidelines advocate for the adoption of a healthy lifestyle, emphasizing a diet rich in fruits, vegetables and whole grains, and routine CRC screening, primarily via colonoscopy or fecal occult blood testing, as the most effective evidence-based interventions to reduce CRC incidence and mortality. GPP

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17. Cervical Cancer

The 2016 IMS guidelines stated that available evidence suggested that MHT does not increase the risk of cervical cancer. Cervical cancer is the fourth most common cancer in the world, affecting females with over 500,000 new cases and 250,000 deaths annually, predominantly in low- and middle-income countries. Preventative measures such as Human Papillomavirus (HPV) vaccination and primary HPV screening have led to the WHO setting a target of eliminating cervical cancer (incidence < 4 /100,000 women per year) by 2030 [1]. Although this may be achievable in high-income countries, significant challenges remain in low-resource settings where the incidence of cervical cancer is the highest.

The vast majority of cervical cancer is HPV-dependent squamous or adenocarcinoma. Data from the Center for Disease Control and Prevention (CDC) and others suggest that up to 10% of cervical cancers are HPV-independent [2], which in some datasets contribute to up to 30% of adenocarcinomas. The incidence of HPV-independent cervical cancer increases with age. The median age of diagnosis of HPV-independent cancer is approximately 60 and is associated with a significantly worse prognosis than the more common HPV dependent variant. The peak incidence of HPV-dependent cancer is between 35 and 45 with a median age of diagnosis of 50 years [2].

Data from the WHI show no increased risk of cervical cancer associated with MHT, however, the number of cervical cancer cases in the entire study was very low (13 in total) [3] which would question the robustness of the data. Observational studies do support these findings [4,5]. Most notably, the European Prospective Investigation into Cancer and Nutrition (EPIC) Study (n=308,036 women) demonstrated that MHT significantly decreased the risk of HPV-dependent cervical cancer (HR 0.3 95% CI 0.1–0.6) [4], with the effect evident up to 5 years duration of therapy. As expected, the effect of MHT on the incidence of squamous cell carcinoma was similar (HR 0.5 95% CI 0.4-0.8), however the number of adenocarcinomas (n=52) in the cohort was too small to draw any robust conclusions. Two historical cohort studies suggested that MHT might increase the incidence of adenocarcinoma of the cervix. A large Finnish population study demonstrated that combined MHT used for 5 years increased incidence of adenocarcinoma of the cervix (HR 1.83, 95% CI 1.24-2.59), however 63% (41/65) of the cases were diagnosed in women over the age of 60 [5]. This older cohort could include a number of HPV-independent cervical cancers and also lower segment endometrial cancers, which can cause a diagnostic dilemma in this age group.

A multicentre case control study from the US also suggested estrogen-only MHT might increase the incidence of adenocarcinoma of the cervix [6], however, less than 10% of the entire study were exposed to MHT, making the robustness of these data very questionable. In conclusion, there is increasing population-based data that MHT does not increase risk of cervical cancer. As the EPIC study is collected from countries where the incidence of cervical cancer is falling [4], the evidence does not fully support a protective impact of MHT on HPV dependent cervical cancer, however, more in-depth research should be performed to assess any link between MHT and HPV independent cervical cancer in older women.

Treatment for cervical cancer regularly induces menopause, as a result of surgery and/or pelvic radiotherapy. A number of international guidelines support the use of MHT in women who have been treated for HPV-dependent cervical cancer irrespective of histological subtype (squamous or

adenocarcinoma) and this use should be consistent with standard menopausal recommendations [7]. Caution should be taken when using MHT after HPV independent cervical cancer.

These recommendations are based on a prospective randomized study published in 1987 [8], which included 120 patients (80 MHT v 40 controls) with stage I or II cervical cancer followed over a five-year period. MHT did not impact on five-year survival or cancer recurrence, but did improve quality of life with reduced menopausal symptoms and reduced radiotherapy-linked complications [8]. Women who have had a hysterectomy can be managed as per standard care. Women who have had external beam radiotherapy +/- brachytherapy should undergo / be prescribed combined MHT. Special emphasis should be placed on bone preservation, particularly in women who received external beam radiotherapy, as pelvic insufficiency fractures are a recognized long term radiation related complication.

It is imperative that these recommendations are implemented, as the use of MHT after cervical cancer is by no means universal. Two independent studies, one from Sweden [9] and on from the US [10] demonstrate that less than 50% of women with premature menopause after cervical cancer were either initially prescribed or continued MHT at five-year follow-up. Initiatives to educate physicians and patients are essential in this cohort of patients.

Recommendations and Key Messages

- MHT may be considered for symptomatic women with HPV-independent cervical cancer, particularly those experiencing premature or early menopause due to treatment. However, due to limited data on safety in this subgroup, careful individualized assessment is recommended, and non-hormonal options may be preferred where risk is uncertain. ⊕⊕⊕◯ C
- MHT is unlikely to be protective against the development of cervical cancer, and more research is required to assess any link between MHT and HPV-independent cervical cancer. GPP

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18. Upper Gastrointestinal Cancer

Liver Cancer

Hormonal effects on liver disease development

Liver cells (hepatocytes) contain sex hormone receptors for estrogens and androgens in the cytoplasm and nucleus [1], and they metabolize sex hormones. In general, compared to men, women show a slower progression of most liver diseases, including progression to fibrosis and cirrhosis [2]. Women also have an overall better outcome from malignant cancer originating from liver cells (hepatocellular carcinoma – HCC). This might be in part due to a stronger immune response in women [3,4], but a direct effect of male and female sex hormones [5,6] as well as indirect effects of differences in lifestyle [7] will play a role.

The development of liver cirrhosis and liver cancer are complex multistage processes. Risk factors for progression are viruses, increase in liver fat through dietary factors, alcohol, or other irritants for the liver. Changes in hormone levels, for example during pregnancy, will affect liver health and lifetime liver risks. Genetic factors will also play a role in HCC development [8]. All steps of liver disease and cancer development are influenced by sex hormones, and at the same time, the liver has an effect on the sex hormones through their metabolism in the liver.

Hepatocellular carcinoma develops mainly in people with liver cirrhosis or hepatitis B virus infection, and estrogen receptors are found in liver cells, including cells of some HCCs [4]. In hepatitis B virus infection, worldwide accounting for about ½ of the HCC cases, cancer frequently develops before the disease leads to cirrhosis. In hepatitis B, there are hormonal influences on the general immune response, but also direct hormonal effects on viral replication [9], influencing cancer development and progression.

Steatotic liver disease (SLD) is a major cause of cirrhosis worldwide, and its risk increases in menopause. Estrogen at pre-menopausal levels is thought to be protective against the risk of metabolic dysfunction in the development of SLD [10]. This is thought to be due to estrogen decreasing hepatic fat stores and increasing insulin sensitivity [11]. Therefore, with estrogen reduction in menopause the risk of developing SLD increases [12]. However, with regard to alcohol consumption, the other main risk factor for SLD, women develop more severe liver damage than men, at lower levels of alcohol intake [13,14]. This is thought to be in part due to liver resident immune cells (Kupffer cells) getting sensitized to endotoxin (lipopolysaccharides) by estrogen and as a result producing pro-inflammatory cytokines [13,15].

Hormonal effects on liver cell (hepatocellular carcinoma) development

Liver cancer is a common and one of the most serious complications of SLD. Development of focal liver lesions including liver cancers which originate from liver cells (hepatocellular carcinomas) is increased in male compared to female patients [16]. In particular, pre-menopausal levels of female sex hormones seem to be protective against HCC [1,17].

Estrogen depresses growth of hepatocytes, including tumor cells, directly through specific sex hormone receptors [18]. The decrease in estrogen during menopause leads to an increase in visceral fat, oxidative stress, inflammation, and progression of fibrosis and cirrhosis [19] as well as rebound

hepatocellular carcinoma growth. One study of patients who had a resection for hepatocellular carcinoma showed that while pre-menopausal women have a reduced risk compared to men, the difference in survival and recurrence of HCC is lost in post-menopausal women [20].

In a retrospective study from Taiwan, over 10.000 patients with chronic hepatitis B infection, but without liver cirrhosis or other malignancies were studied. In women who took MHT for at least 3 months, MHT was associated with significantly lower risk of HCC and all-cause mortality (but not cirrhosis development) [21]. In another Taiwanese study, 1022 women treated for hepatitis C who took HRT for at least 90 days were compared with 1022 women who did not receive HRT. Similarly to the hepatitis B study, in case of hepatitis C infection, women on MHT had a lower crude and lower adjusted hazard ratios of developing a HCC over 7 year follow up [22]. Moreover, women on HRT presented a reduced risk of mortality from HCC [22]. From a Korean study on over 40,000 women with a diagnosis of endometriosis, the beneficial effect of HRT was found in estrogen as well as combined estrogen and progesterone therapy [23]. Therefore, it appears that MHT can at least partly counteract the negative effects of estrogen reduction in postmenopausal women [17,22]. This beneficial effect of MHT seems to be particularly evident in early stages of cancer [24].

Hormonal effects on biliary epithelial cell cancer development and conclusion

There is a lower prevalence of liver cancers originating from biliary epithelial cells (cholangiocellular carcinoma - CCA) compared to cancers from liver cells (HCC). Although there is a biologically plausible effect that biliary cancers are also influenced by sex hormones, there is less evidence for this compared to HCC [25], and further studies are needed to confirm this assumption/theory.

In post-menopausal women the risk of liver cancer is higher than in pre-menopausal women. MHT weakens, to some extent, the effect of menopausal hormone changes with regard to cancer development [17,22,26]. However, it is unclear what the size of the effect / the actual impact of HRT is compared to the very well evidenced modification/reduction of major risk factors such as alcohol and metabolic dysfunction, which improve survival in postmenopausal women [27,28].

Gastric Cancer

Multiple observational studies suggest a protective association between menopausal hormone therapy (MHT) and gastric cancer [29-32]. A 2024 Korean cohort study by Han et al. found significantly reduced gastric cancer risk in MHT users (HR 0.65; 95% CI 0.52–0.82), particularly in current users and those with longer duration of therapy [30]. These findings align with previous data from Baek et al and pooled analyses showing a 20–35% lower risk of gastric cancer in MHT users compared to non-users [31,32].

Reproductive factors also appear to influence risk. Later menopause, higher parity, and longer fertility duration have been consistently associated with reduced gastric cancer incidence, suggesting a cumulative, protective estrogen effect [29,31].

Biological plausibility is supported by mechanistic studies showing that estrogen may inhibit gastric tumorigenesis through anti-inflammatory actions, modulation of the PI3K/AKT pathway, and effects on Helicobacter pylori–associated inflammation and carcinogenesis [33,34].

While most data come from observational studies, the consistency of results across populations and study designs supports a potential protective role for estrogen in gastric cancer [29-31].

Esophageal Cancer

Evidence linking MHT to esophageal cancer is more limited and varies by subtype.

Adenocarcinoma

Esophageal adenocarcinoma (EAC) is markedly more common in men. Several studies suggest a potential hormonal influence. Circulating hormone studies, such as those by Petrick et al., have shown inverse associations between estradiol levels and EAC risk [34,35]. Cohort studies examining MHT use in relation to OAC have produced inconsistent findings [36,37]. A UK Biobank analysis by McMenamin et al. (2021) found no significant association between circulating sex hormones and EAC [35].

Squamous Cell Carcinoma

For esophageal squamous cell carcinoma (SCC) in menopause hormone therapy users the evidence is weaker. While estrogen receptor expression has been identified in SCC tissue [38-40], no consistent epidemiological association with MHT has been demonstrated. Smoking, alcohol consumption, and dietary factors continue to be the predominant drivers of SCC risk [41].

Recommendations and Key Messages

- Postmenopausal women should be managed similarly to men. ⊕⊕⊕◯ C
- MHT might be of some benefit to prevent and slow down the progression of (early) hepatocellular carcinoma, thereby improving the outcome. ⊕⊕⊕◯ C
- For most women, lifestyle modification will have a larger benefit on liver-related outcomes compared to MHT. ⊕⊕⊕⊕ B
- Observational studies suggest that MHT may be associated with a reduced risk of gastric cancer in postmenopausal women. ⊕⊕◯◯ C
- Reproductive factors associated with prolonged estrogen exposure, such as later menopause and higher parity, are also linked to a lower risk of gastric cancer. ⊕⊕◯◯ C
- For esophageal cancer, the evidence for a protective effect of MHT is less clear with some indication of a possible protective association for adenocarcinoma. ⊕⊕◯◯ C
- Mechanistic studies provide biologic plausibility for a protective role of estrogen in liver and gastric cancer and highlight the need for further research in this area. GPP

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19. Quality of Life – Psychosocial / Psychological / Cognitive health

(Methodology:) For each section, consideration was given to previous position statements from the IMS [1] and The Menopause Society [2]. To ensure the inclusion of the subsequent clinical trials, we then conducted a review of the studies published since 2022 on menopausal hormone therapy (MHT) and their key outcomes (quality of life, anxiety, cognition, depression, depressive symptoms, and sleep) in peri- and postmenopausal women. Abstracts were screened and filtered using the following exclusion criteria: basic science (i.e. animal models), breast cancer research, reviews, books, systematic reviews, non-English papers, commentaries, retracted papers, study protocols, not randomized controlled trials (RCTs), or published prior to 2022. Texts were excluded at the full-text stage if they were not relevant to the specific topic (QOL, anxiety, cognition, depression, and sleep), were not relevant to hormone therapy, did not use validated or standardized outcomes, had a hormone therapy treatment time of < 4 weeks, evaluated non-systemic hormone therapy only, evaluated hormone therapy with an additional pharmaceutical intervention, included premenopausal women only, did not use a placebo-controlled design, or used mixed hormone therapy (except estrogen with progesterone).

Quality of Life

When considering the effects of MHT on quality of life (QOL), it is important to differentiate between global QOL, health-related QOL, and menopause-related QOL [3]. Global QOL refers to the sense of daily functioning and achievements in the context of a specific culture and value system, including life satisfaction and overall well-being. Health-related QOL refers to the aspects that are most likely to be affected by changes in health status, as assessed by the Utian Quality of Life Scale (UQOL) [4]. Menopause-related QOL refers specifically to those aspects of QOL that are most likely to be affected by menopause, commonly assessed with tools such as the Menopause-specific Quality of Life questionnaire (MENQOL) [5] and the Menopause Rating Scale (MRS) [6]. While global QOL and health-related QOL generally do not differ between women taking MHT and those on placebo, MHT is associated with improved menopause-related QOL [3]. A recent series of randomized placebo-controlled trials have shown that low and ultra-low-dose MHT improved menopause-related QOL scores among European and Chinese women [7-10]. A clinical trial has examined estetrol (E4), a natural estrogenic steroid found in the fetal liver which has been shown to be effective for relieving menopause symptoms [11] and found a short-term improvement in menopause-related QOL at the highest dosage (15mg) compared to placebo [12]. As participants in these clinical trials were symptomatic (i.e. vasomotor symptoms, genitourinary symptoms), the benefits of MHT on health-related quality of life was explained by symptom relief.

Anxiety

More than half of midlife women experience anxiety symptoms, including tension, nervousness, and irritability [13-15]. Evidence suggests that there is an increased risk for depressive symptoms and potentially, depressive disorders, across the menopause transition (MT), specifically for those with a prior history of depression [16,17]. Though anxiety is highly comorbid with depression, it remains unclear if anxiety symptoms and anxiety disorders worsen in the peri- and/or postmenopause compared to the premenopause, particularly as most research in the field has been cross-sectional in nature and utilized unstandardized measures of anxiety [18].

Limited longitudinal work suggests that the risk of high anxiety symptoms increases across the MT in women with low anxiety symptoms at baseline. In contrast, for those with high anxiety at baseline, anxiety symptoms remain elevated across the MT but are unrelated to menopause stage. This suggests that the MT may confer vulnerability to anxiety symptoms in non-anxious women [19].

Evidence suggests that anxiety symptoms are more strongly related to menopause symptoms, particularly vasomotor symptoms (VMS), than menopause stage [19]. Moderate to severe anxiety symptoms often co-occur with VMS and/or poor sleep [20,21]. Given the efficacy of MHT for the treatment of menopause symptoms, MHT should be considered in relation to anxiety symptoms and anxiety disorders across the MT [2].

There are no randomized trials of MHT in women with anxiety disorders, so its effects in this population are unknown. Initial evidence from two clinical trials conducted in healthy peri- and postmenopausal women suggests a benefit of estrogen therapy (ET) for anxiety symptoms, even when accounting for VMS [22,23]. In perimenopausal women, the efficacy of transdermal estradiol for anxiety symptoms was highest in those whose anxiety symptoms at baseline correlated reliably with week-to-week variability in estradiol [23]. However, given the limited clinical trial data, there is insufficient evidence to recommend the use of any for MHT for the treatment of anxiety symptoms and anxiety disorders in peri- and postmenopausal women.

Cognition

Large-scale longitudinal studies show that women experience declines in cognition, particularly verbal memory abilities, across the menopause transition [24-27]. While some evidence indicates a transient verbal memory deficit that ameliorates in the postmenopause [25], other studies suggest that this cognitive decline persists into the postmenopause [24,27]. Three large, randomized placebo-controlled clinical trials reported that MHT neither improves nor harms cognitive abilities when used in the early postmenopause [22,28,29]. These effects are observed with conjugated equine estrogen (CEE) alone [22,28], CEE with medroxyprogesterone acetate (MPA) [28], transdermal estradiol [29], and oral estradiol, indicating that results are independent of formulation. A 10-year post-trial follow-up of one of these clinical trials showed that hormone therapy use, specifically CEE or oral estradiol, in the early postmenopause had no long-term effects on cognition [30]. Notably, there are no large-scale, randomized clinical trials of hormone therapy in women with the primary indication for hormone therapy, namely moderate-to-severe VMS. Nor are there randomized clinical trials of hormone therapy in women in the perimenopause, though that is the reproductive stage in which memory declines occur [24-27].

Several clinical trials show that hormone therapy has no benefits to cognition when initiated in women older than 65 years [29,31-35]. Among older women, CEE-MPA combination has been shown to have adverse effects on cognitive performance [36,37], suggesting that certain hormone therapy formulations may confer greater risk for cognitive decline at this age.

The impact of MHT on cognition likely differs for women who undergo surgical menopause. A meta-analysis showed that women who undergo bilateral oophorectomy before the onset of menopause have faster rates of cognitive decline [38]. For this population specifically, small clinical trials indicate that hormone therapy may maintain processing speed, working memory, and verbal memory abilities when initiated immediately after hysterectomy with bilateral oophorectomy [39,40].

Depression and Depressive Symptoms

The menopause transition is a window of vulnerability for the development of depressive symptoms and depressive disorders, though most women who develop depressive disorders during this time have a prior history of depression. Women with a history of depression are at high risk for recurrence of depressive disorders during the menopause transition, and as such should be evaluated and treated according to the established clinical guidelines (e.g. selective serotonin/norepinephrine reuptake inhibitors, cognitive behavioural therapy, other psychotherapies, etc.) [15,16].

Menopause symptoms such as sleep disturbance and VMS commonly co-occur with depressive symptoms across the menopause transition. Sleep disturbance is associated with a higher incidence of depressive symptoms, as well as next-day negative mood and lower next-day positive mood [41,42]. Nighttime VMS are also associated with a higher number of depressive symptoms, with sleep disturbances partially explaining this association [41]. Additionally, VMS are associated with higher ratings of the next-day negative mood and lower ratings of the next-day positive mood, but only in women with low to moderate depressive symptoms [42,43]. Therefore, treatment of VMS with MHT should be considered in women with depressive symptoms.

The efficacy of MHT for the treatment of depressive symptoms and depressive disorders across the menopause transition differs by menopause stage and depression status. In healthy perimenopausal women, a prominent symptom of depression, anhedonia, was associated with variability in estradiol levels, and decreased following estrogen therapy (ET) [23]. In perimenopausal women with depressive disorders, depressive symptoms are reduced following ET [44,45]. Response rates to ET are similar to those of antidepressants and ET demonstrates efficacy in both the presence and absence of VMS [45]. In a head-to-head clinical trial of cyclical hormone therapy (0.45 mg/d oral CEE) or 50 µg/d transdermal estradiol daily plus 200 mg/d micronized progesterone for the first 12 d of each month) in healthy postmenopausal women, depressive symptoms improved following administration of CEE but not transdermal estradiol [22]. Depressive symptoms do not improve in postmenopausal women with depressive disorders following administration of ET [46]. ET plus intermittent micronized progesterone (EPT) prevented the development of clinically significant depressive symptoms in a clinical trial of euthymic peri- and postmenopausal women [47]. In peri- and postmenopausal women with depressive disorders, improvements in depressive symptoms were seen in relation to improvements in sleep but not VMS; perimenopausal but not postmenopausal showed improvements in depressive symptoms in relation to increases in estradiol [48]. ET might augment clinical response to antidepressants, including SSRIs and SNRIs, in perimenopausal women with VMS [49]. Greater understanding of the efficacy of EPT for treatment of depressive symptoms and disorders across the menopause transition is needed.

Sleep

Sleep disturbance is a common symptom reported across the menopause transition, affecting 40-69% of women [50]. During this time, sleep disturbance is characterized primarily by greater wakefulness [51]. VMS during sleep are strongly associated with sleep disturbance [52,53]. Sleep disturbance can lead to changes in mood and cognition, and increase risk of Alzheimer's disease, hypertension, cardiovascular disease, diabetes, and all-cause mortality [41,42,54-57]. As such, poor sleep exacerbates other menopause symptoms and is detrimental to work performance and overall health [58,59].

A network meta-analysis of randomized trials concluded that oral combined MHT as well as CEE plus bazedoxifene reduced sleep disturbance in women with VMS, but that MHT did not improve sleep

more generally [60]. Transdermal estrogen has also been found to improve sleep quality in perimenopausal women, beyond its ability to alleviate VMS and other symptoms [61]. Use of micronized progesterone before bedtime can improve sleep-onset latency but appears to be neutral in affecting total sleep duration and sleep efficiency in postmenopausal women [62]. Evidence suggests that midlife women experiencing sleep disturbance have altered heart rate variability (HRV), indicating autonomic arousal during sleep, but hormone therapy in peri- and postmenopausal women did not improve HRV compared to placebo [63]. Cognitive behavioural therapy for insomnia (CBT-I) is recommended as first-line treatment of sleep disturbance.

Recommendations and Key Messages

- In women experiencing bothersome menopause symptoms, MHT improves menopause-related quality of life. ⊕⊕⊕◯ B
- In women experiencing bothersome menopause symptoms, MHT does not improve global or general health-related quality of life. ⊕⊕◯◯ C
- HCPs should be aware that the menopause transition may represent a window of vulnerability for the development of anxiety symptoms in non-anxious women. Anxiety symptoms may remain elevated across the menopause transition in women with high anxiety, but menopause stage is unrelated to anxiety symptoms. VMS appear more strongly related to anxiety symptoms than menopause stage. ⊕⊕◯◯ C
- HCPs should be aware that anxiety symptoms often co-occur with menopause symptoms, including moderate to severe VMS and poor sleep. ⊕⊕◯◯ C
- The effects of MHT on anxiety disorders is unknown. ⊕⊕◯◯ C
- There is insufficient evidence to recommend the use of MHT use for the treatment of anxiety symptoms in perimenopausal and postmenopausal women. ⊕⊕◯◯ C
- Except in premature ovarian insufficiency or early menopause, MHT is not recommended to prevent or treat cognitive decline at any age. ⊕⊕⊕⊕ A
- In women older than 65 years, CEE+MPA may be harmful to cognition. ⊕⊕⊕◯ B
- MHT has neutral effects on cognition in the natural early postmenopause. ⊕⊕⊕⊕ A
- MHT may confer benefits to cognition when initiated immediately after hysterectomy with bilateral oophorectomy. ⊕⊕⊕◯ B
- The effects of MHT on cognition among women with moderate-to-severe VMS and in perimenopausal women are unknown. KM
- There is some evidence that ET improves anhedonia in perimenopausal women without depressive disorders. It is yet unknown whether ET improves depressive symptoms more generally in perimenopausal women. ⊕⊕◯◯ C
- ET may improve depressive symptoms in perimenopausal women with depressive disorders in both the presence and absence of VMS. Efficacy of ET in this population appears similar to that of antidepressants. ⊕⊕◯◯ C
- ET may be effective in lowering depressive symptoms in postmenopausal women without depressive disorders. ⊕⊕◯◯ C
- ET is not efficacious for the improvement of depressive symptoms in postmenopausal women with depression. ⊕⊕◯◯ C

- MHT may prevent the emergence of clinically significant depressive symptoms in euthymic women across the menopause transition, but more evidence is needed before recommending MHT for this use. ⊕⊕◯◯ C
- In midlife women with depressive disorders, improvements in mood were associated with improvements in sleep but not VMS. ⊕⊕◯◯ C
- ET might augment clinical response to antidepressants in perimenopausal women with VMS. ⊕⊕◯◯ C
- HCPs should be aware that sleep disturbance is a common menopause symptom, particularly wakefulness after sleep onset. ⊕⊕⊕⊕ A
- HCPs should be aware that night-time VMS are strongly associated with awakenings. ⊕⊕⊕⊕ A
- HCPs should be aware that poor sleep across the menopause transition is related to numerous health outcomes, including changes in mood and cognition, as well as Alzheimer's disease, hypertension, cardiovascular disease, diabetes and all-cause mortality. ⊕⊕⊕◯ B
- MHT improves sleep in women with VMS but does not appear to affect sleep in midlife women more generally. ⊕⊕⊕◯ B
- Transdermal estrogen may improve sleep quality in perimenopausal women, beyond its effects on VMS and other symptoms. ⊕⊕◯◯ C
- Micronized progesterone taken before bedtime improves various sleep outcomes in postmenopausal women. ⊕⊕◯◯ C
- Cognitive behavioural therapy for insomnia (CBT-I) is recommended as first-line treatment of sleep disturbance in women across the menopause transition. ⊕⊕⊕⊕ A

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20. Androgen Therapy

Androgen physiology in women

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 (LCMS) has enabled the measurement of testosterone at low levels, but the issue of inter-assay variability with this methodology persists. Studies that have measured with precision sex hormones in women have shown that blood levels of testosterone and the pre-androgens, androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) peak in the third decade of life and then progressively decline with age until the 5th decade of life [1,2]. Testosterone blood levels appear to remain stable during the menopause transition [1,3]. DHEA and DHEA-S progressively decline with age [1,4], while testosterone increases from the 6th to 7th decade of life [4,5].

The clinical interpretation of androgen levels in women is limited by the synthesis of testosterone and dihydrotestosterone in peripheral target tissues so that serum levels may not accurately reflect androgen exposure at the cellular level, and, by individual variations, in androgen receptor sensitivity and responsiveness. Established pathological causes of low testosterone include primary ovarian insufficiency [6], bilateral oophorectomy at any age [1], hypopituitarism [7], adrenal insufficiency and iatrogenic suppression of ovarian function before menopause [8].

Testosterone and female sexual function

The associations between testosterone measured by LCMS and sexual function have been reported for premenopausal women [9,10]. In the study that took into account menstrual stage, age, body mass index, smoking and demographic variables, testosterone was positively associated with orgasm and sexual self-image, while DHEA and androstenedione were associated with sexual desire [10]. Notably, none of the hormones explained more than 4% of the variation in any sexual outcome. Robust data regarding midlife sexual function remains lacking.

A meta-analysis of placebo-controlled RCTs demonstrated testosterone therapy has moderate efficacy for postmenopausal hypoactive sexual desire dysfunction (HSDD), with statistically significant improvements in sexual satisfaction, desire, arousal, pleasure, orgasm and sexually related distress [11]. These effects are seen in naturally and surgically menopausal women, with and without concurrent MHT [11]. Women presenting with HSDD should have a full biopsychosocial assessment and any identified causes of HSDD, such as dyspareunia, depression, medication side-effects, relationship issues and health problems affecting the woman or her partner, should be addressed before initiating testosterone therapy [12].

As there is no diagnostic test to identify likely responders, testosterone administrations should always be considered a trial of therapy [12]. At physiological doses benefits emerge after 4 to 6 weeks [13], and it is recommended that the treatment be discontinued if there is no significant benefit by 6 months.

Although testosterone blood levels decline prior to menopause, there is insufficient data to support the use of testosterone for HSDD in premenopausal women [11].

Androgenic side-effects of testosterone therapy are dose-related and the Global Consensus Position Statement on Testosterone for Women recommends that the treatment is limited to transdermal

therapy with doses, and where possible formulations, adjusted to women [12]. The available data suggest that treatment with transdermal testosterone in doses that approximate physiological testosterone concentrations for premenopausal women may cause (or worsen) acne, trigger hair growth and weight gain in some women, but no data confirm adverse cardiometabolic or endometrial effects [11]. An increase in breast cancer risk has not been noted [11], however no data are available for RCTs beyond 2 years for this outcome.

Presently, a testosterone women-specific formulation has been approved by regulators in Australia, the UK, New Zealand and South Africa. Internationally endorsed guidance regarding the prescribing and monitoring of testosterone therapy for women are provided by the open access Global Consensus Position Statement on Testosterone for Women [12].

Testosterone and other health outcomes

Recent systematic reviews of observational studies have shown testosterone blood levels are not associated with mood [14], cognitive function [15], or muscle mass and performance [16]. The reviews highlighted that the available data in these areas are not suitable for meta-analysis due to methodological flaws, such as inconsistent research approaches or lack of precision in testosterone measuring. In women beyond the age of 70 years, testosterone concentrations, measured by LCMS, below the 25th centile have been associated with a greater likelihood of ischemic cardiovascular events [17], depressive symptoms [18], and lower limb joint replacement [19]; testosterone has been positively associated with bone density in women over the age of 67 years [20).

Meta-analyses of blinded RCTs of testosterone versus a comparator, of at least 3 months of duration, have shown no significant benefit or harm of testosterone therapy for psychological and general wellbeing, depressive symptoms, cognitive performance, cardiovascular events, BMD or muscle mass and performance [11]. A subsequent literature search since that study identified one RCT of women with anti-depressant resistant major depression, which showed no benefit of transdermal testosterone over placebo [21]. A separate meta-analysis reported no benefit of testosterone for well-being or depressive symptoms of women after surgical menopause [22]. It is noteworthy that the studies providing data for cognitive performance and muscle mass and performance were all small, of short duration, and measured inconsistent outcomes [11] such that the findings should be considered inconclusive. In addition, most of the studies providing data for testosterone effects on depressive symptoms excluded women with moderate to severe symptoms [11]. However, the subsequent study of testosterone for moderate to severe depression showed no benefit [21]. There are no RCT data for testosterone and fracture prevention.

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 [23, 24]. 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 [25].

Treatment of vulvovaginal atrophy

Androgen receptors, aromatase (which converts testosterone to estradiol) and 5a-reductase isotypes 1 and 2 (convert testosterone to dihydrotestosterone) are present throughout the urogenital tract [26]. One of the earliest applications of testosterone therapy was for vaginal atrophy [27].

Intravaginal testosterone administered alone or with vaginal estrogen has been shown to improve dyspareunia, sexual desire, lubrication and satisfaction compared with placebo [28,29]. Beneficial effects have been seen with its administration three times/week [29]. While these studies are promising, larger research is required before intravaginal testosterone can be recommended in clinical practice.

Intravaginal prasterone, a product name for DHEA, has been shown to have favorable effects on the vaginal epithelium and is approved in many countries for the treatment of postmenopausal dyspareunia due to vulvovaginal atrophy (VVA) [30]. It is recommended that the 6.5mg prasterone vaginal insert is self-administered daily, with one study showing no benefit over placebo with twice weekly use [31]. A pilot study on the efficacy of prasterone on breast cancer survivors demonstrated that the alternate day administration of prasterone in 10 women taking aromatase inhibitor therapy after breast cancer, did improve sexuality and vaginal health [32], however larger studies are required to evaluate the safety of this therapy after breast cancer.

Recommendations and Key Messages

- Studies to date have shown that testosterone blood concentration declines across the reproductive years, does not change acutely with natural menopause and increases from the seventh decade of life, while DHEA blood levels decline progressively with age. ⊕⊕⊕◯ B
- Most available immunoassays lack precision for measurement of testosterone within the female range and reference ranges differ between assays; there is no blood level below which a woman can be designated as being testosterone deficient. ⊕⊕⊕⊕ A
- Postmenopausal HSDD is an evidence-based indication for a therapeutic trial of a physiological dose of testosterone therapy. ⊕⊕⊕⊕ A
- All women presenting with sexual concerns should have a comprehensive biopsychosocial assessment and modifiable factors addressed before testosterone is prescribed. ⊕⊕⊕⊕ A
- Available data do not support the prescription of testosterone for women for any symptom or condition (other than postmenopausal HSDD) or for disease prevention. Evidence quality ranges from ⊕⊕⊕◯ B to ⊕⊕⊕⊕ A
- The available data do not support the use of systemic DHEA therapy for the treatment of female changes in sexual function or any other clinical symptoms or condition. ⊕⊕⊕◯ B
- Intravaginal DHEA (prasterone) is an effective option for the treatment of dyspareunia secondary to VVA. ⊕⊕⊕⊕ A

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21. Perimenopausal Contraception

Contraception in the perimenopause has an important role to play in midlife women's health. Collaboration with the College of Sexual & Reproductive Healthcare (CoSRH) in the UK has facilitated access to an existing guideline on contraception in women over 40 [1]. This guideline provides valuable recommendations for perimenopausal women, potentially requiring a method of contraception to protect against unplanned pregnancy. It is also relevant for women who wish to use hormonal contraception for its non-contraceptive benefits. Common symptoms of perimenopause include irregular and heavy menstrual bleeding (HMB) [2,3] and vasomotor symptoms, both of which can be improved with hormonal contraception.

Introduction

Women over 40 years of age experience a natural decline in fertility; however, the risk of unintended pregnancy persists until menopause. Pregnancy at advanced maternal age is associated with increased risks, including miscarriage, ectopic pregnancy, and congenital anomalies. In addition, the risk of chronic health conditions, such as hypertension and type 2 diabetes, increases as women get older. Uterine fibroids become more prevalent with age and can be associated with HMB in the perimenopause [4].

Perimenopausal women have unique contraceptive needs and access to comprehensive contraceptive counselling can ease the transition from reproductive to post-reproductive life [5].

When is contraception no longer needed?

Contraception can be stopped at age 55, as spontaneous conception after this point is extremely rare. For users of copper intrauterine devices (Cu-IUD) and barrier methods, contraception can be discontinued after two years of amenorrhoea between ages 40–50, or after one year of amenorrhoea in women over the age of 50. Combined Hormonal Contraception (CHC) (pills, patch, and vaginal ring) and progestogen only injectables should be discontinued by age 50, due to potential increased risks in relation to cardiovascular and bone health. Progestogen only pills (POP) and progestogen only implants may be continued until age 55. For amenorrhoeic women over 50 using progestogen-only methods, a single FSH level >30 IU/L supports discontinuation of contraception after further 12 months. A Cu-IUD inserted at or after age 40 can remain in place until menopause, and a 52-mg Levonorgestrel intrauterine device (LNG-IUD) inserted at or after age 45 can be used for contraception until age 55. If used as part of MHT, a 52-mg LNG-IUD needs to be replaced by five years.

Contraceptive Choice - Recommendations for Midlife Women

CHC

CHC is suitable for healthy, non-smoking women without cardiovascular risk factors, until age 50. The different options within this group (pills, patch and vaginal ring) may help manage vasomotor symptoms, preserve bone mineral density (BMD), and control heavy menstrual bleeding. Continuous use (omitting hormone free interval) can be beneficial for women with menstrual migraine or premenstrual dysphoric disorder (PMDD), where the preferred progestogen is drospirenone. CHC is associated with an increase in risk of venous thromboembolism (VTE), myocardial infarction (MI), and cardiovascular accident (CVA), particularly with advancing age and additional risk factors. There is a 2- to 4-fold increase in the risk of developing pre-diabetes and type 2 diabetes, particularly in women

with metabolic risk factors including obesity, polycystic ovary syndrome (PCOS) and a family history of type 2 diabetes mellitus [6]. Newer combined oral contraception (COC) formulations containing natural estrogens (e.g. estradiol valerate, estradiol (E2) and estetrol (E4)) may offer safety benefits for older women when compared with ethinyl estradiol (EE). Pills containing both estradiol valerate and estradiol are acceptable methods of contraception for perimenopausal women in terms of their metabolic effects and risk profile [7,8]. A pill containing estetrol (E4), (produced by the human fetal liver during pregnancy) and drospirenone have recently come to market. E4 is 100 times less potent than E2, which is less potent than EE and it may have a more neutral effect on lipids and haemostasis than EE containing COCs. However, more data is required before widespread use can be adopted in suitable perimenopausal women.

Progestogen-Only Methods (Progestogen Only Pill, Progestogen only Implant, Progestogen-only Injectables, Levonorgestrel Intrauterine Devices (LNG-IUD)

Progestogen-only methods are appropriate for most women over 40 and may induce amenorrhoea, and control symptoms in women with perimenopausal HMB, including women with endometriosis and adenomyosis. However, irregular bleeding is common and may lead to over-investigation in this age group. Progestogen only implants and POPs can be continued until age 55. In the UK, POPs containing desogestrel (75 mcg) are used preferentially, due to a 12-hour missed pill window. A POP containing drospirenone (4 mg) has recently become available, with a 24:4 regime and a 24-hour missed pill window, potentially improving efficacy and bleeding pattern. Injectable progestogens can be associated with a reduction in BMD and caution is advised in women over age 45, with discontinuation advised by age 50. Some countries use depot medroxyprogesterone acetate (DMPA) as a treatment for women with perimenopausal irregular bleeding, with the added benefit of provision of contraception [9].

A 52-mg LNG-IUD is effective for contraception for up to 8 years and if inserted at or after age 45 can remain in situ until age 55. A 52-mg LNG-IUD is licensed to provide contraception, manage HMB and provides highly effective endometrial protection, as the progestogenic arm of MHT [10,11]. It has particular benefits for perimenopausal women experiencing dysfunctional uterine bleeding (DUB) and is suitable for women with adenomyosis [12]. If using estrogen with a 52-mg LNG-IUD, the device should be changed at least every 5 years.

Copper Intrauterine Device (Cu-IUD)

A Cu-IUD inserted at or after age 40 can remain in situ until menopause. However, there is no beneficial effect on bleeding, which can be particularly problematic in perimenopausal women.

Sterilisation

Women considering sterilisation should be informed that long-acting reversible contraception (LARC) is more effective, reversible, and offers additional health benefits. Given the natural decline in fertility with age, the benefits of permanent contraception are limited at this life stage.

Barrier Methods

Barrier methods include male and female condoms, diaphragms, and cervical caps. These are suitable at any age and have few contraindications. Their effectiveness may be higher in women over 40, due to declining fertility and more consistent use. Condoms provide protection against sexually transmitted infections (STIs).

Menopausal Hormone Therapy (MHT) and Contraception

There are several ways in which MHT and contraception can overlap. CHC may be used in eligible women under 50 as an alternative to MHT for vasomotor symptom control. A 52mg LNG-IUD can provide both contraception and endometrial protection as part of MHT regimes. POPs, progestogen only implants, copper IUDs and barrier methods of contraception can be used alongside standard MHT regimes.

Hormonal Contraception and Risk of Neoplasia

Hormonal contraception is associated with a small increase in breast cancer risk during current or recent use. This risk declines after discontinuation and is minimal in absolute terms. CHC is linked to long-term reductions in the risk of endometrial and ovarian cancers. Prolonged use of medrogestone, medroxyprogesterone acetate, and promegestone was found to increase the risk of intracranial meningioma [13].

Hormonal Contraception and Cardiovascular Risk

CHC is linked to an increased risk of VTE, myocardial infarction, and CVA, especially in women with additional risk factors such as smoking, hypertension and obesity. There in an increase in risk with increasing age and with higher doses of estrogen. Progestogen-only methods (other than progestogen only injectables) are not associated with an increase in cardiovascular risk and are preferred in older women. As cardiovascular risk naturally increases with age, an individual risk assessment is recommended.

Hormonal Contraception and Bone Health

CHC may help maintain bone mineral density (BMD) during the perimenopause. DMPA is associated with a modest, reversible reduction in BMD due to its hypoestrogenic effect, but injectables are not associated with worse BMD outcomes in older women [14-16]. Other progestogen only choices have not been shown to adversely impact BMD. Relugolix is a gonadotrophin-releasing hormone antagonist (GnRH receptor antagonist) indicated to shrink uterine fibroids and reduce HMB in premenopausal women. Relugolix in combination with estradiol and norethisterone (Ryeqo®) provides contraception, when it has been used for 4 weeks at an appropriate dose and is associated with minimal BMD changes [4].

Conclusion

Women in midlife require personalised contraceptive counselling that accounts for declining fertility, evolving health risks, and perimenopausal symptoms. Many methods offer dual benefits of pregnancy prevention and menopausal symptom management [17]. Method selection should be guided by individual preference, medical history, risk assessment and treatment goals.

Recommendations and Key Messages

- Considering contraceptive choices is important for perimenopausal women. Contraception counselling should be tailored to the individual, considering comorbidities, risk factors and personal preference. ⊕⊕◯◯ C
- A change in bleeding pattern is common in perimenopausal women. Any 52-mg LNG IUD, some POPs and CHC decrease bleeding and are associated with an improvement in quality of life, but long-term use of CHC increases the risk of prediabetes and type 2 diabetes mellitus in women with metabolic risk factors. ⊕⊕⊕◯ B
- A COC containing nomegestrol acetate (NOMAC) with 17 β-estradiol (E2) is not associated with an increase in VTE risk compared to levonorgestrel containing COCs and can be considered for perimenopausal women. ⊕⊕⊕⊕ A
- The benefits and risks of different progestogen-only contraceptive methods need to be considered when prescribing, such as benefits associated with a reduction in bleeding and risks to bone health with depot medroxyprogesterone acetate (DMPA). ⊕⊕⊕⊕ A
- There is a modest reversible reduction in BMD with DMPA, which is not exacerbated by menopause. This has not been observed with any other contraceptive methods including relugolix, a gonadotropin-releasing hormone antagonist, in combination with estradiol and norethisterone (NETA). ⊕⊕◯◯ C
- Relugolix, in combination with estradiol and NETA is a treatment for uterine fibroids and endometriosis, which provides contraception, reduces bleeding and pain influencing quality of life, and maintains bone density. ⊕⊕⊕◯ B
- A small increase in the risk of developing breast cancer with both CHC and progestogen-only contraceptive methods has been reported. These data are not specific to perimenopausal women and risk declines with cessation, with no breast cancer related risk after 10 years. ⊕⊕⊕⊕ A
- Use of a 52-mg LNG IUD with low-dose estrogen in perimenopausal women appears to be the most effective option to alleviate perimenopausal symptoms and to provide long-term health benefits such as endometrial protection and bleeding control. For women not eligible for a 52-mg LNG IUD or who decline this option, COCs or progestogen-only contraceptive choices are an option but may have fewer additional benefits for perimenopausal women. ⊕⊕⊕◯ B

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22. Premature Ovarian Insufficiency (POI) / Early Menopause (EM)

Premature ovarian insufficiency (POI), also known as primary ovarian insufficiency and previously as premature ovarian failure, is both an endocrine and reproductive disorder with significant psychological impact, and can be a devastating diagnosis for young women [1]. POI is defined as loss of ovarian activity before the age of 40 [2]. The age 40 was chosen as less than 2 standard deviations of the mean age of spontaneous menopause [1,2]. POI is characterized by oligo-/amenorrhoea with elevated gonadotrophins and low estradiol [2]. Early menopause refers to menopause under the age of 45, occurring in up to 12% of the population, and has less severe but still significant long-term health risks [2,3]. Globally, women report delayed diagnosis and dissatisfaction with care and care variation [2], which prompted the updated 2024 POI guideline [1,2], a partnership between IMS, European Society of Human Reproduction and Embryology (ESHRE), American Society for Reproductive Medicine (ASRM) and Monash Centre for Health Research and Implementation (MCHRI).

The global prevalence of non-iatrogenic POI was previously thought to occur in 1% of the population under 40 and 0.1% in women under the age of 30, however recent meta-analyses have reported it amounts to approximately 3.5% which varies according to region, human development index (higher in developing countries) and ethnicity (higher in Hispanic and African American compared to Asian women) [2,4]. Two recent studies report an increase in POI incidence in young women under age 20 in Israel [5] and Finland [6]. The prevalence of iatrogenic POI may be growing due to: (i) increasing survival rates following chemo- and radiotherapy and (ii) increasing rates of cancer risk reducing bilateral oophorectomy, with increased detection of genes such as BRCA1/2 associated with cancer [1].

Risk factors for POI include: genetic predisposition / cause, family history of POI or early menopause, low body weight, smoking, lower socioeconomic status, being a twin, nulliparity, shorter menstrual cycles, geographic variation, autoimmune disease, environmental pollutants and medical treatments, such as chemotherapy (Table 1) [1,2,7-9]. Up to 30% of women with idiopathic POI have a family history of early menopause or POI, with menopausal age being heritable [10]. Studies have suggested an incidence of POI as high as 18 fold in a cohort of Utah first-degree relatives [11].

Clinical Presentation and Diagnosis

The clinical presentation of POI varies, both within and between individuals and also regarding the cause of POI [1]. Symptoms and signs of POI include primary or secondary oligo-/amenorrhoea, infertility, symptoms of estrogen deficiency and those related to the underlying causes [1,2]. Primary amenorrhoea is more common in women with an underlying genetic cause of POI. POI symptoms may be intermittent or fluctuate in severity, reflecting changes in ovarian activity in those with non-iatrogenic POI. Intermittent resumption of ovarian activity may occur in over 25% of women, especially in the first few years after the diagnosis [12]. However, some women, especially younger ones with primary amenorrhoea, may not experience any symptoms related to low estrogen level.

The diagnosis of POI should be considered in any female under the age of 40 presenting with any of the following: oligo-/amenorrhoea for at least 4 months, infertility or estrogen deficiency symptoms. In contrast to previous guidelines, updated POI diagnostic criteria are: amenorrhoea or menstrual disturbance for at least four months and one elevated follicle stimulating hormone level (FSH) >25 [1,2]. FSH concentration >25 IU/L represents a value greater than the physiological peak observed in premenopausal women and will encompass women with POI due to autoimmune causes. Symptoms of low estrogen are not required for diagnosis of POI. If there is diagnostic uncertainty, the FSH level

should be repeated after 4-6 weeks or, alternatively, anti-mullerian hormone (AMH) level can be checked [2]. Although low levels of AMH (<0.5ng/ml or 3.6pmol/L) are associated with an increased risk of POI [1,2,13], AMH check is not recommended as the primary diagnostic test as it conveys no advantages to FSH in this context [2,14]. However, AMH assessment may be considered where the diagnosis is inconclusive. AMH is currently not recommended for prediction of POI [2,14,15]. There is ongoing research into additional biomarkers for POI [16,17]. The diagnostic usefulness of ovarian biopsy outside the context of a research setting is unproven.

The diagnosis of POI can be a devastating one and women may experience a range of emotions. Factors which can lessen the negative impact of POI on quality of life were reported in a scoping review and included compassionate clinicians, prompt and sensitive revelation of the diagnosis, individualized care, timely provision of information, providing time to answer questions and continuity of care [18]. Social support (family, friends and peer-peer) and counselling were also important [18].

Women with POI are now recognized to be at increased risk for premature multi-morbidity and mortality and face a decreased quality of life [1,2,18,19]. They have an increased risk of infertility, cardiovascular disease (including ischemic heart disease, stroke, heart failure, atrial fibrillation), diabetes mellitus, dyslipidemia, metabolic syndrome, impaired endothelial function, hypertension, osteoporosis, impaired muscle parameters including sarcopenia, decreased cognition and dementia, parkinsonism, dry eye disease, poorer psychological health (anxiety, depression, poor self-esteem/ body image) and diminished sexual well-being [1,20-26]. The causes of POI also influence / determine health risks: studies have reported increased risks of adverse cardiometabolic or bone parameters in those with iatrogenic POI versus spontaneous or idiopathic POI [1,20,27,28], and mixed findings regarding Turner Syndrome associated POI versus normal karyotype spontaneous POI [29,30]. Childhood cancer survivors with POI have an increased prevalence of metabolic syndrome compared to cancer survivors without POI or controls [31].

Pathophysiology and Causes

POI represents a continuum of antral follicular reduction (reduced ovarian reserve where women menstruate but ovaries do not respond well to stimulation, with reduced oocyte retrieval and fewer successful pregnancies) to less than 1000–2000 oocytes, ultimately leading to premature hypogonadism [3]. From 700,000–1,000,000 oocytes at birth, the oocyte/ follicle survival and original number of oocytes determine the reproductive lifespan, typically through 400 ovulated cycles [32]. POI occurs due to the premature loss of oocytes, including impaired oogenesis, impaired folliculogenesis and maturation, accelerated destruction and atresia. Bilateral oophorectomy before the age of 40 causes surgical POI.

POI is a heterogenous disorder and can be either spontaneous or iatrogenic. In many cases (39-67%) of spontaneous POI the cause is unknown ('idiopathic POI') [1]. However, increased genetic testing will help to identify a cause, as shown in a recent study where whole exome sequencing added to the usual diagnostic investigations for idiopathic POI (Figure 1) detected POI pathogenic gene variants in 16% of patients [33]. The causes of POI are shown in Table 1.

The genetic etiology of POI is complex with chromosomal anomalies and gene variants (predominately X chromosome but also autosomal) implicated, with variable penetrance and inheritance (Table 1). Chromosomal anomalies are identified in approximately 10-13% of individuals with POI [1,34]. The commonest abnormal karyotype associated with POI is Turner Syndrome [30]. The advent of new

genetic testing has identified over 100 nuclear gene variants associated with POI [1,35] and variants in the mitochondrial gene *MT-CO1* reported in a Chinese POI cohort [36]. However, not all identified gene variants have been established as pathogenic [1,37]. Data from international cohorts has identified gene variant positivity in approximately 25% of sporadic POI, 30-40% familial POI and over 50% in syndromic POI[2,38], with a variation observed between ethnicities and within families [39]. Implicated genes are involved in all stages of oocyte and follicle development/ function, metabolism, immune function, mitochondrial function, RNA metabolism and translation. The role of non-coding RNA in the pathogenesis of POI is an emerging area of research. The POI genotype-phenotype may be modified by interaction with other alleles, epigenetics, RNA, proteome and environmental factors such as smoking [40-42]. Gene variants common to POI and POI associated co-morbidities have also been identified [43-45]. The most common single gene variant associated with POI is premutation (55-200 CGG repeats) of the Fragile X messenger ribonucleoprotein 1 gene (*FMR1*) identified in 1-5% of women with sporadic POI and up to 13% of familial POI [1]. The *FMR1* premutation occurs in 1/150-300 European/USA women (lower frequency in Asian populations [1,46]) and 20-30% of these women develop POI [1]. Less commonly, POI may be syndromic, observed in 8.5% of POI patients in one European cohort [1]. Clinical presentation of syndromic POI varies with the causative gene, including endocrine/ neurosensorial/ cardiovascular symptoms, inborn errors of metabolism, ovario-leukodystrophy, and potential susceptibility to tumours/cancers [1,47].

A systematic review and meta-analysis found that iatrogenic causes occurred in 11.2% of cases of POI [4]. The survival of paediatric cancer patients has led to an increase in iatrogenic POI cases, with 8% of patients developing POI acutely and 18.6% by age 40 [7]. Chemotherapeutic agents used for benign and malignant disease, such as anthracyclines (especially with additional taxanes), alkylating agents (e.g. cyclophosphamide), procarbazine, cisplatin, melphalan and busulfan have been linked to gonadal toxicity [1,7]. Recovery of ovarian function after chemotherapy and radiation depends on the type, age at time of administration, dosage, and location of radiation [48]. Allogenic bone marrow transplant (currently utilized for hematologic malignancies and genetic conditions such as sickle cell disease) utilize radiation and chemotherapeutic conditioning prior to transplantation, which renders over 80-90% of recipients infertile [49]. Management of benign gynaecologic disorders has evolved with more ovarian conservation. However, surgical causes of POI remain common and include bilateral salpingo-oophorectomies for inherited BRCA for cancer prophylaxis, removal of ovarian tumours and bilateral endometriomas or torsions, and inadvertently through uterine embolization. Bilateral oophorectomy was the commonest cause of POI in a cohort of USA women from a single county [50].

Autoimmune disorders occur more frequently in women with POI, both preceding and after POI diagnosis [2,51-53]. The variable prevalence of autoimmune diseases in women with POI, reported in 3-37% cases (systematic review 10.5% of cases [4]), reflects differences in populations, methodology, and diagnosis (antibody positivity versus clinical diagnosis) [1]. Autoimmune disorders associated with POI include: autoimmune thyroid disease (20% of women), polyglandular autoimmune syndrome, and other immunologic conditions such as adrenal insufficiency (6%–20%) (Table 1) [1,24,51-54]. Autoimmune regulator (*AIRE*) gene mutations cause autoimmune polyglandular syndrome type 1. Women with autoimmune POI may have higher inhibin B and AMH levels compared to other women with other etiologies [1]. Significant genetic causal relationships have recently been identified between coeliac disease, vitiligo, systemic lupus erythematosus, Addison's disease and POI [55]. Adrenal antibodies are

positive in 4% of women with autoimmune POI, and adrenal 21 hydroxlase antibody is the most specific for autoimmune POI [2] (Figure 2).

Other rare etiologies of POI (<1%) include infectious causes (e.g. mumps, HIV), metabolic disorders (e.g. galactosemia) and environmental toxins including exposures to organic pollutants, phthalates, heavy metals such as cadmium, thallium, arsenic, polycyclic aromatic hydrocarbons, and cigarette smoke [1,8] (Table 1). Ultimately a combination of multiple factors may precipitate POI.

Management

The diagnosis of POI can be very distressing and the impact on the patient and family members needs to be considered. Prompt diagnosis, sensitively conveyed with provision of information and support is important [1,2]. Once the diagnosis is made then comprehensive evaluation is needed to investigate cause (Figure 2) and address symptoms, psychological health, chronic disease risk, hormone therapy choice, sexual function and fertility needs (Figure 1) [2]. Counselling of relatives especially where there is a genetic cause of POI identified is important [2]. As women with POI have an increased risk of multi-morbidity, long term monitoring is needed (Figure 1) [1,2].

Lifestyle

There is a lack of evidence specifically investigating the effects of lifestyle interventions on the relief of menopause symptoms and long-term health in women with POI [56]. However, given the favorable data derived from women at the usual age of menopause (see Section 3 Lifestyle), treatment of POI with hormone therapy (HT) and any other medical interventions should be underpinned by optimization of lifestyle, diet and exercise, minimisation of alcohol and avoidance of smoking to enhance quality of life and prevent chronic disease[1,2].

Hormone Therapy

Observational studies indicate that use of HT in women with POI or early menopause is associated with reduced risks of mortality and chronic diseases including osteoporosis and dementia [1,25]. Inconsistent findings of risk reduction or no effect are reported in relation to cardiometabolic disease [1,26] RCT data are limited to the effect of HT on symptoms and surrogate markers versus disease outcomes; however, improvement in symptoms, bone density, lipids, endothelial function, blood pressure and body composition are observed with HT [1] (Table 2). Therefore, to manage symptoms and reduce the risk of morbidity and mortality, an individualized HT should be initiated promptly (unless contraindicated), whether there are estrogen deficiency symptoms or not, and continued until at least until the usual age of menopause (Figure 1). When women with POI reach the usual age at which menopause occurs, the need for continued HT should be based on a personalised risk-benefit assessment and current evidence.

Regimen: Women with POI generally require higher doses of estrogen compared to women at the usual age of menopause to fully alleviate menopause associated symptoms and to achieve optimum bone mineralisation, which reflects the physiological environment for this age group. Some women may need to start at a lower dose to avoid adverse effects with titration upwards. In non-hysterectomised women, it is imperative that concomitant progestogen is used with estrogen for endometrial protection. The dose of progestogen should be proportional to the dose of estrogen used [57]; the type of progestogen prescribed should depend on individual risk/benefits and with taking into consideration the fact that most data are derived from studies in women using HRT at usual

menopause age (see Section 4a VMS: MHT). Although theoretically there are benefits from the use of transdermal compared to oral estrogen (see Section 4a VMS: MHT), there are few data specific to the POI population. Hormone replacement therapy (HRT) should not be regarded as being contraceptive unless estrogen is combined with the 52mg levonorgestrel intrauterine device or with an oral progestogen in a contraceptive dose. Suggested regimens are shown in Table 3, adapted from ESHRE POI Guideline of standard v POI HRT regimens.

Combined estrogen (ethinyl-estradiol or estradiol) and progestogen contraceptive pills (COCs) can be used in women desiring contraception until the expected time of the menopause, but long-term prospective data regarding their impact on bone and cardiovascular outcomes are lacking (see Section 21 Perimenopausal Contraception). If the estrogen containing COCs is used in women with POI, the hormone free interval should be minimised or avoided altogether to avert the risks of recurrence symptoms and bone loss [1].

Risks: There are few data specific to women with POI and risks of HT are predominately extrapolated from studies of women with usual menopause age or premenopausal women using COC (see Section 21 Perimenopausal Contraception). The impact of HT on the incidence of breast cancer has been poorly studied. Physiological replacement of estrogen is unlikely to increase the risk of breast cancer compared to women with normal endogenous estrogen production. Short term use of HRT after cancer risk reducing bilateral salpingo-oophorectomy in BRCA1/2 mutation carriers does not significantly attenuate the benefits of the surgical procedure [1].

Monitoring: response to treatment is assessed primarily clinically by evaluating symptoms relief, bone density and uterine development. Measurement of estradiol can be helpful if there is persistence of symptoms, adverse effects, or concern regarding inadequate bone protection [1]. Typical mean serum estradiol levels of approximately 200-400 pmol/l (which represent physiological mid follicular estradiol levels) is considered adequate. The rationale for recommending higher doses of HT is that, as well as symptom relief, there appears to be a dose–response effect regarding cardiovascular and bone benefits, although there are few dose–response trials of HT in POI [58].

Barriers to HT: Despite the recognition of POI as an indication for HT [59], one of the biggest barriers to prescribing it in POI/EM is the lack of availability of HT options and resource implications, particularly in low and middle income countries [60]. Also, a recent study in women with iatrogenic POI/EM following cervical cancer showed that fear of cervical cancer recurrence (even though not considered hormone sensitive), fear of breast cancer or other malignancy dissuaded / discouraged some women from using HT [61]. This highlights the importance of adequately counselling women with POI about the pros and cons of HT, thus empowering them to make an informed decision.

Testosterone Therapy

Although POI is associated with lower testosterone levels versus age matched controls [62], the decreased sexual function reported in women with POI [24] is often complex and multifactorial. In women with low libido, especially in oophorectomized women, testosterone therapy can be offered (see Section 5 GSM and Section 20 Androgen Therapy). There is a lack of evidence for other potential indications for testosterone therapy such as cognitive functions, mood, energy and musculoskeletal health [63,64]; however, studies are in progress to investigate these issues. There are inadequate data regarding the role of DHEA to make a recommendation for its use in women with POI/EM (see Section 20 Androgen Therapy).

Non-hormonal pharmacologic and non-pharmacologic approaches

The use of HT, in certain scenarios, may be considered undesired or contraindicated e.g. in women with POI following hormone sensitive malignancy. However, there is a lack of efficacy and safety data for non-hormonal pharmacological and non-pharmacological interventions specific to women with POI [1] and evidence must be extrapolated from studies of women across a wide range of menopause ages, often after iatrogenic interventions for breast cancer and other malignancies (see Section 23 Non-pharmacological interventions and Section 4b VMS: Non-hormonal Pharmacological).

Complementary and alternative medicine (CAM)

There are few well conducted studies on CAM therapies in POI and the data, which mostly derive from women at the standard menopause age, are rather inconsistent [1, 2]; (see Section 24 Complementary Therapies). Recent systematic reviews and meta-analyses reported potential benefits of acupuncture [65] and Chinese herbal medicine, Er-xian decoction for POI [66], but evidence is limited due to high risk of bias and study heterogeneity. A recent systematic review and meta-analysis of the role of acupuncture in anxiety and depression in patients with POI reported that acupuncture was more beneficial than HRT for depressive symptoms [67]. However, complementary therapies should not replace HT, unless HT is contraindicated for medical reasons or patient choice.

Fertility and POI

Infertility is often the most distressing aspect of POI diagnosis for a young woman. The spontaneous conception rate after diagnosis is 5%–15% [12]. Newer techniques and therapies have reported slightly higher conception rates, but these findings require further scrutiny. Currently, only oocyte/embryo donation or adoption provide the most successful options for family building [2], with 41% of women ultimately having a family [68]; however, these alternatives may not be acceptable to all women.

Oocyte donation pregnancies are associated with hypertensive disorders, risk of miscarriage, and increased caesarean section rates - the risk varying with underlying cause of POI [1,2,30,69]. Other interventions such as hormone therapy, pre-stimulation oral contraceptive use, gonadotropins, GnRH agonists, DHEA, steroids, and testosterone stimulation have not been shown to improve fertility rates beyond spontaneous pregnancy predictions [1,2].

Fertility preservation techniques for women / persons at risk of POI (but not with confirmed POI) include: oocyte/ embryo/ ovarian tissue cryopreservation, and use of GnRH agonists (especially in case breast cancer patients, however with little benefit for hematologic cancers) [1,2,48,70,71]. In case of oncological patients, these should receive individual onco-fertility counselling advising on risk assessment, relocation of ovaries, cryopreservation of oocytes or embryos prior to anticancer treatments [70] or ovarian tissue cryopreservation in pre-pubertal girls [71]. Novel therapies have been studied which stimulate dormant oocytes via stem cell transplantation or activate primordial follicles via physical or chemical manipulation [72]; however, methodological flaws (such as lack of controls or inadequate sample size) impose limitations on final conclusions [1]. A 2024 meta-analysis (five studies with a total of 164 patients and high risk of bias), reported significant follicular development (and subsequent live birth rate of 20%) after follicle activation therapies in women with POI, with lower baseline FSH, shorter duration of amenorrhoea/POI and presence of follicles [73]. Platelet-rich-plasma (PRP) injections into the ovaries, which contain growth factors, demonstrated to have improved aspects of follicular activation and inhibited apoptosis [74]. However, randomized controlled trials

(RCTs) of PRP have so far yielded disappointing results [1,75]. Nonetheless, with greater understanding of ovarian biology, hope for restoration of ovarian function does exist.

Models of Care

There is limited research on the best models for optimal care delivery for POI patients [76]. Clinical care may be best provided in interdisciplinary clinics that address the multiple medical and psychosocial issues associated with POI [40,77,78]. Online co-designed information resources are available and should be provided [1]. Referral to support groups such as the Daisy Network (www.daisynetwork.org) is recommended.

Recommendations and Key Messages

- POI is both an endocrine and gonadal condition defined as loss of ovarian activity in women younger than age 40 years. Early menopause (menopause between ages 40 and 45 years) also has similar ramifications. KM
- The diagnosis of POI is based on four months or more of menstrual disturbance/amenorrhoea and one FSH level >25 IU/L, as per the ESHRE 2024 POI guideline. GPP (www.eshre.eu/Guidelines-and-Legal/Guidelines/Premature-ovarian-insufficiency)
- FSH assessment should be repeated after 4–6 weeks if there is diagnostic uncertainty. FSH testing for the diagnosis of POI does not have to be timed to a specific day of the menstrual cycle. GPP
- HCPs should be aware that POI is not a rare condition and occurs in up to 3.5-3.7% of the global population. ⊕⊕⊕⊕ A
- HCPs should be aware that the clinical presentation of POI is variable, including oligo-amenorrhoea, symptoms of estrogen deficiency, infertility or underlying cause of POI. Symptoms may be minimal, intermittent and/or vary in severity. ⊕⊕◯◯ B
- HCPs should be aware that POI is a heterogeneous disorder with multiple etiologies, the most common being idiopathic. With the advent of more precise genetic assessments, more genetic causes are being found. ⊕⊕◯◯ A
- HCPs should inform women that POI is associated with menopausal symptoms, infertility, decreased quality of life, poorer psychological and sexual well-being, and increased risk of cardiovascular disease, osteoporosis, impaired muscle parameters, cognitive decline, dementia and Parkinsonism. Untreated POI is associated with decreased life expectancy. ⊕⊕◯◯ A
- Investigation for causes of POI should include hormone analysis, screening for autoimmune causes and pelvic ultrasound. Where available, karyotyping, fragile X premutation testing and additional genetic testing, such as next-generation gene sequencing, are suggested after appropriate counselling. ⊕⊕◯◯ B
- It is important to inform the woman of the diagnosis of POI with empathy in a sensitive and caring manner. Women should be provided with evidence-based information and counselling (www.eshre.eu/Guidelines-and-Legal/Guidelines/Premature-ovarian-insufficiency). GPP
- Comprehensive evaluation after diagnosis is recommended to personalize treatment and optimize quality of life and to maintain long-term health. GPP
- Women with POI should be advised about lifestyle, diet and exercise to optimize cardiometabolic and bone health, although POI-specific data are lacking. ⊕⊕◯◯ C

- HCPs should be aware that the main treatment of POI is HT (hormone replacement therapy (HRT) or COC) which should be initiated promptly and continued at least until the usual age of menopause. ⊕⊕⊕◯ A
- HT should be offered whether there are symptoms or not, for primary prevention to reduce the risks of morbidity and mortality. ⊕⊕◯◯ A
- HCPs should be aware that HRT should not be regarded as being contraceptive unless combined with an intrauterine progestogen-releasing device. ⊕⊕⊕◯ A
- HCPs should be aware that women with POI may require higher doses of HT than those at the usual age of menopause to achieve adequate symptom control and bone protection. ⊕⊕◯◯ B
- A progestogen should be used in combination with estrogen in all women with POI with an intact uterus for endometrial protection, and the dose of progestogen should be increased when higher doses of estrogen are used. ⊕⊕◯◯ A
- Women with POI can be informed that there is no evidence that the risk of breast cancer with HT is higher than in women of the same age group with normal ovarian function. ⊕⊕○○ C
- A biopsychosocial approach should be used by HCPs for diagnosing and managing HSDD in women with POI, and consideration should be given to prescribing testosterone therapy where appropriate. ⊕⊕◯◯ C
- Non-hormonal pharmacologic and non-pharmacologic therapies can be considered where HT is contraindicated but women should be informed that evidence specific to POI is lacking. ⊕◯◯◯ C
- HCPs should be aware that there is insufficient evidence for efficacy and safety to recommend routine use of complementary therapies in women with POI. ⊕⊕◯◯ B
- Women with POI should be informed that, currently, there are no interventions which can reliably increase ovarian activity and natural conception rates. ⊕⊕⊕◯ A
- Women with POI who do not achieve a pregnancy naturally should be informed that, currently, the best fertility options are oocyte/embryo donation with assisted reproduction technology (ART) or adoption. ⊕⊕⊕◯ A
- Regular review and multidisciplinary care are suggested for the optimal management of women with POI. GPP

Table 1. Known causes of premature ovarian insufficiency.

- Genetic
    - Chromosome anomalies:
        - mainly X chromosome aneuploidy and mosaicism, X structural abnormalities or X-autosomal translocations, e.g.Turner Syndrome
    - Nuclear gene variants:
        - *FMR1* premutation
        - Other gene candidates, e.g.*NOBOX, FSHR, BMP15, FOXL2, GDF9, NR5A1, STAG3* [35]
        - Syndromic POI, e.g. autoimmune polyglandular syndrome 1 (Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy) caused by mutations in the *AIRE* gene
    - Mitochondrial genes *MT-CO1* [36]
    - Non-coding RNA [34]
- Metabolic e.g. Galactosemia (*GALT* gene) [47]
- Autoimmune diseases
    - autoimmune thyroid disease, polyglandular syndromes and other immunologic conditions such as adrenal insufficiency, alopecia, vitiligo, pernicious anemia, coeliac disease, hypoparathyroidism, Crohn's disease, idiopathic thrombocytopenia, primary biliary cirrhosis, glomerulonephritis, myasthenia gravis and multiple sclerosis, rheumatologic conditions such as rheumatoid arthritis, lupus, psoriasis
- Infections
    - mumps, HIV, cytomegalovirus, varicella, tuberculosis, shigella, malaria, herpes zoster
- Environmental toxins
    - smoking, organic pollutants, phthalates, heavy metals such as cadmium, thallium, arsenic, polycyclic aromatic hydrocarbons
- Iatrogenic
    - chemotherapy and radiotherapy
    - bilateral oophorectomy (surgical POI)
    - hysterectomy without oophorectomy/uterine artery embolization/ endometriosis surgery, unilateral oophorectomy [79]

Table 2. Summary of indications for HT in women with POI. Reproduced from ESHRE (2024) Evidence-based guideline: premature ovarian insufficiency [2]

TABLE V SUMMARY OF INDICATIONS FOR HORMONE THERAPY (HT) IN WOMEN WITH POI

Symptoms or Sequelae of POI	Indication for HT	Supporting recommendation
Vasomotor symptoms	**YES**	HT is indicated for the treatment of vasomotor symptoms in women with POI.
Genitourinary symptoms	**YES**	Offer vaginal estrogen therapy to improve genital, sexual and urinary symptoms. Women with POI may be offered vaginal estrogen therapy if genitourinary symptoms are not fully relieved by systemic HT.
Life expectancy	**YES**	Women with POI should be offered HT at least until the usual age of menopause as primary prevention to reduce risk of overall morbidity and mortality
Skeletal health	**YES**	HT is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.
Muscle health	**Uncertain**	The effect of HRT on muscle parameters in women with POI is uncertain but may be of benefit.
Cardiovascular health	**YES**	Estrogen therapy has beneficial cardiometabolic effects which can influence cardiovascular disease risk. Non-use of HT is associated with an increased risk of cardiovascular events and mortality. HT is therefore recommended until the usual age of menopause.
Quality of life	**Uncertain**	HT has a positive impact on quality of life in women at usual age of menopause. There are minimal data regarding women with POI, but HT may be of benefit
Sexual function	**YES**	Where HT has been prescribed for other indications to women with POI, it may ameliorate sexual function, acknowledging the effect is generally small.
Neurological function	**YES**	HT may be recommended in women with POI to protect neurological function even in the absence of menopausal symptoms.
Fertility treatment	**YES**	HRT in higher doses creates a favourable hormonal environment for fertility intervention such as replacement of embryos in oocyte donation IVF.
Puberty Induction	**YES**	HRT is indicated for normal pubertal development and skeletal maturation

Table 3. Summary of HRT options: standard and POI regimens modified with permission from Panay, N et al. 2020 [58].

HRT type	***Sequential combined HRT***		***Continuous combined HRT***	
Per 24 hours or day	*Low/standard doses*	*'POI' doses*	*Low/standard doses*	*'POI' doses*
Estradiol type				
Patch (transdermal, µg/24h	**25–50**	**75–100**	**25–50**	**75–100**
Gel sachet (transdermal, mg)	**0.5–1.0**	**2.0–3.0**	**0.5–1.5**	**2.0–3.0**
Gel pump (1 metered dose = 0.75 mg)	**1–2**	**3–4**	**1–2**	**3–4**
Transdermal spray (1.53mg per spray)	**1-2**	**3-4**	**1-2**	**3-4**
Oral (mg)	**1.0–2.0**	**2.5–4.0**	**1.0–2.0**	**2.0–4.0**
Progestogen				
Micronized progesterone (oral/per vagina, mg)	**100–200**	**≥ 200 (e.g. 300–400)**	**100**	**≥ 200**
Dydrogesterone (oral, mg)	**10**	**20**	**5.0**	**10**
Medroxyprogesterone acetate (oral, mg)	**5.0*-10**	**10-20**	**2.5**	**5.0**
Norethisterone acetate (oral, mg)	**2.5–5.0**	**2.5–10**	**1.25–2.5****	**2.5-5.0**
Levonorgestrel intrauterine system (LNG IUD)	**20 µg/day sufficient for low/standard and POI doses (52mg LNG IUD)**			
17 beta-estradiol (E2)/progestogen fixed dose combined preparations				
E2/micronized progesterone (oral, mg)	**n/a**	**≥ 2.0/≥ 200**	**1.0–2.0/100–200**	**3.0–4.0/300–400**
E2/norethisterone acetate (transdermal) (µg)	**25–50/85–170**	**75–100/255–340**	**25–50/85–170**	**75–100/255–340**
E2/dydrogesterone (oral, mg)	**1.0–2.0/10**	**2.0/10**	**0.5–1.0/2.5–5.0**	**3.0–4.0/7.5–10**
E2/norethisterone acetate (oral, mg)	**1.0–2.0/1.0**	**3.0–4.0/2.0–4.0**	**0.1–2.0/0.5–1.0**	**3.0–4.0/1.5–2.0**

Notes

- The table does not show all available options globally. Some regimens are achieved off label on first principles by halving/doubling/combining regimens especially for the fixed dose combined regimens.
- Higher doses of estradiol usually required in POI but, to assess tolerance or if adverse effects, lower doses may be used initially.
- Variation globally as to what doses perceived as low, medium, and high, e.g. North America 0.5 mg E2 is low dose, 1 mg E2 is standard dose, and 2 mg E2 is high dose.
- Sequential regimens require 12-14 days progesterone/progestogen per cycle for endometrial protection – this may need modification depending on tolerance.
- Endometrial safety is less assured with micronized progesterone used for > 5 years.
- Progesterone/progestogen doses shown are the minimum effective for endometrial protection given current data.
- Endometrial safety data are lacking for the minimum effective dose of progestogen/progesterone with higher estrogen doses.

* The licensed dose for sequential MPA is 10mg; 5mg is a compromise low dose for progestogen intolerant patients on low dose estrogen

** A 1 mg dose of norethisterone acetate is adequate for standard-dose continuous combined HT but is only available in a fixed dose combination with E2, hence 1.25–2.5 mg doses (¼ to ½ of a 5 mg tablet).

Figure 1. Management algorithm for POI. Reproduced from ESHRE (2024) Evidence-based guideline: premature ovarian insufficiency [2]

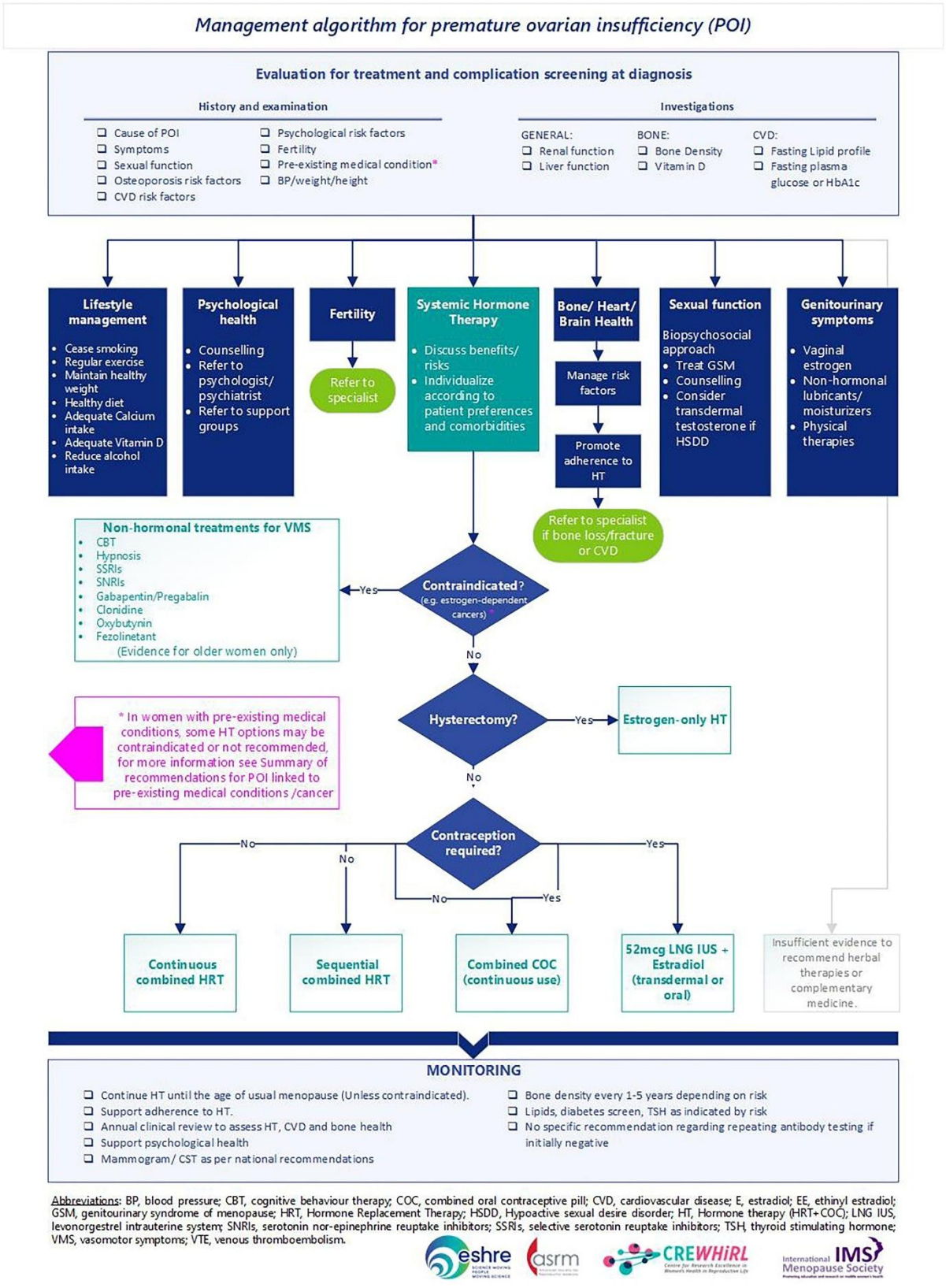
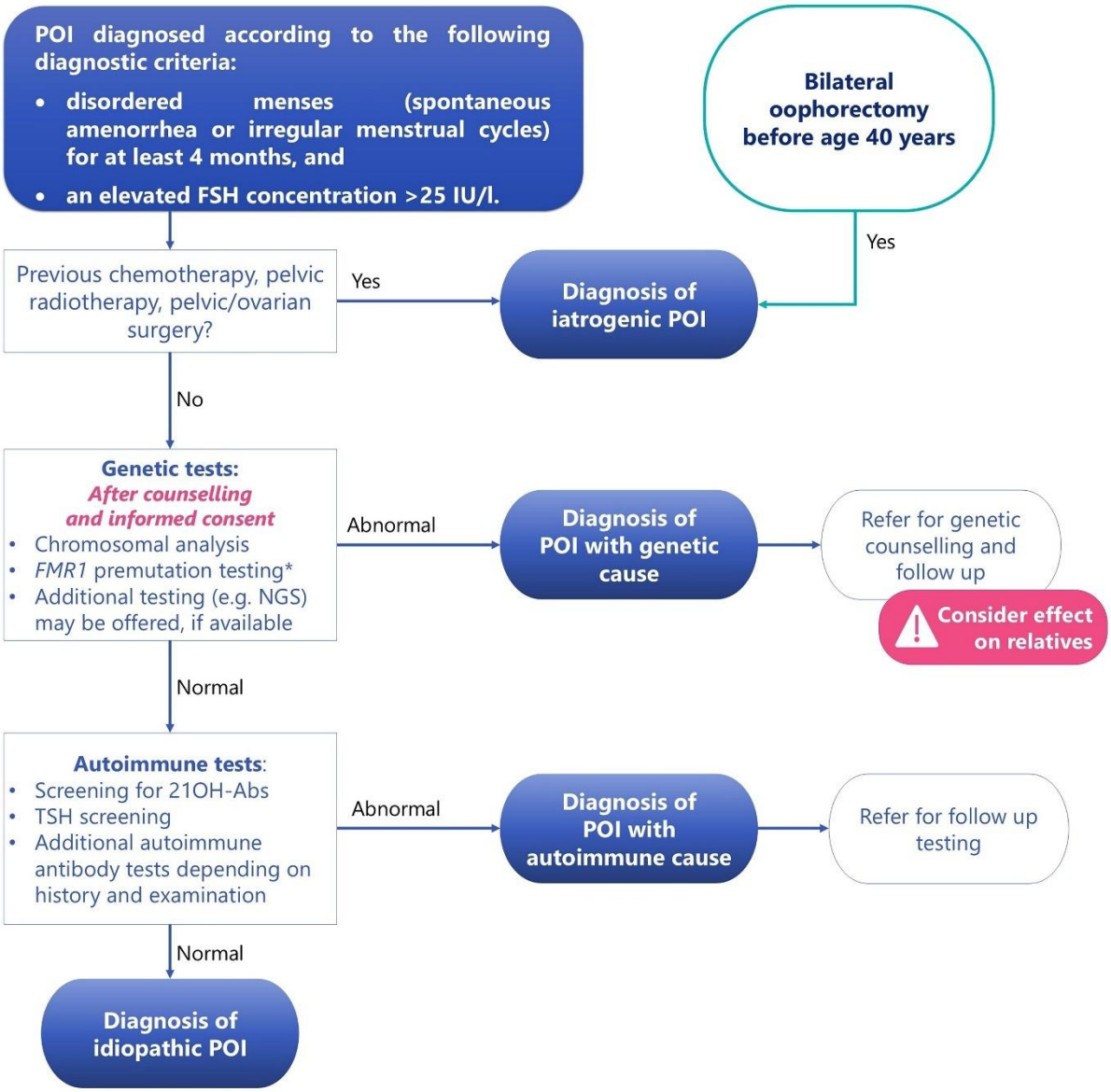


Figure 2. Summary of the recommendations on diagnosis of premature ovarian insufficiency (POI) reproduced from ESHRE (2024) Evidence-based guideline: premature ovarian insufficiency [2]



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23. Non-pharmacological Interventions

Cognitive Behavioral Therapy (CBT)

In menopausal women who choose not to use menopause hormone therapy (MHT), or in whom MHT is contraindicated, vasomotor symptoms (VMS) can be extremely problematic. Whilst a wide range of non-hormonal therapies have been recommended to help alleviate VMS, in many cases data is either lacking or has demonstrated lack of efficacy [1]. In contrast, a wide range of studies have shown that cognitive behavioral therapy (CBT) is effective in alleviating troublesome VMS. CBT is a brief therapy of 4-6 weekly sessions that is theory and evidence based. It is acceptable to women and effectively reduces the impact of VMS, albeit less than MHT, whilst also improving sleep and quality of life [2]. RCTs have found that CBT is effective in reducing the 'bother' associated with moderate to severe VMS in both women undergoing normal menopause and breast cancer survivors [3,4]. MENOS 1 compared CBT group (one 90-minute session per week for 6 weeks) with usual care in 96 breast cancer survivors. CBT significantly reduced the problem rating of VMS after 9 weeks with the benefit persisting for 26 weeks [3]; MENOS 2 compared weekly CBT group with usual care amongst 140 menopausal women experiencing 10 or more problematic VMS per week. CBT significantly reduced problematic VMS compared to controls by 6 weeks with the benefits persisting for 26 weeks. Additional benefits included improved mood and quality of life and improved emotional and physical functioning [4].

However, the data found that generally these effects are modest [2]. One hypothesis is that CBT does not affect the physiological processes of VMS but changes the way in which VMS are perceived and understood [1]. Mindfulness and relaxation techniques that are part of a CBT intervention may also help decrease the severity of VMS [4,6]. Studies have shown that CBT is equally effective when provided through different interventions, including self-help and face-to-face therapy, group sessions, online/internet therapy [7], as well as phone counselling [6,8]. This suggests that CBT is useful for women unable or unwilling to attend therapy in person, and in reducing costs of medical visits in resource-stressed public healthcare systems in low-income countries [8]. A single blind RCT targeting both VMS and depressive symptoms found that women randomized to receive the CBT-Meno protocol (sessions with psycho-education and CBT approaches), compared to no active intervention, had a significant decrease in troublesome VMS and depressive symptoms, which was maintained beyond 3 months of treatment [9]. Although there were some significant limitations, including a no treatment comparison rather than comparing the CBT-Meno with an active therapy intervention, the treatment was well-received by CBT-Meno participants who found it highly effective [9].

A comprehensive review found that there is Level 1 evidence to recommend CBT as a non-hormonal therapy to alleviate troublesome VMS in both menopausal women and breast cancer survivors [1].

Clinical Hypnosis

Clinical hypnosis is a psychotherapy which enhances the interaction between the mind and body, creating deep relaxation, heightened concentration and focused attention. Hypnosis is a helpful therapeutic intervention for dealing with certain chronic issues, including pain management, anxiety, depression and VMS [1,10]. Several studies have demonstrated that clinical hypnosis is as effective in alleviating VMS as CBT) [11]. A single-blind randomized controlled trial (RCT) found that hypnosis (delivered 5 times per week for 12 weeks) significantly reduced hot flush frequency, compared with a control group receiving structured attention therapy. Importantly, this study used both subjective (Hot

Flush Symptoms Diary) and objective measures (sternal skin conductance monitoring system) to ascertain severity and prevalence of VMS [12]. A subsequent analysis of the study found that the participants' expectations of the efficacy of clinical hypnosis were unrelated to the effects of the intervention [13]. A retrospective analysis found that hypnotherapy was effective in alleviating VMS also when delivered using a smartphone application, suggesting widespread accessibility to hypnotherapy for women suffering from this condition [14]. A scoping review found that both CBT and clinical hypnosis are effective in reducing VMS frequency in normal menopausal women as well as in breast cancer survivors, with additional benefits such as improved sleep and psychological quality of life. Responses varied with the 'hypnotisability' of participants, although even those less hypnotisable eventually enjoyed some benefit. This review also found that while CBT may help manage both stress and cognitive reactions to VMS, clinical hypnosis significantly reduced both the frequency and severity of vasomotor symptoms [11].

Weight Loss

Weight gain is a major concern of women in midlife. Studies have shown that women gain around 1kg per year during the perimenopausal years, even though weight gain is not related to menopausal status. However, the menopausal decline in estrogen results in central adipose accumulation and transition from a gynecoid to android pattern of fat distribution. Longitudinal data have shown that obese women may have a greater prevalence and severity of VMS than those with a normal BMI [1,15,16]. This appears to be due to the thermoregulatory role played by body fat which protects against the expected heat dispersion of hot flushes [17]. The relationship between body fat and VMS may differ according to menopause stage, with greater adiposity causing an increase in VMS in early perimenopause before switching to a protective role when estrogen significantly declines in the late menopause transition [17]. Studies have shown that changes in body adiposity, body mass index (BMI) and waist circumference are related to the presence and severity of VMS [18]. Data from SWAN found an association between VMS prevalence in women who continued to gain weight and increased central obesity over 10 years. A pilot study comparing a behavioural weight loss intervention to normal care amongst overweight or obese menopausal women experiencing at least 4 hot flushes per day discovered that the intervention group lost significantly more weight and a greater reduction in questionnaire reported hot flushes compared to controls. Reductions in weight and hot flushes were significantly correlated [17]. At present there are no data regarding the use of glucagon-like peptide-1 (GLP-1) agonists for weight loss and their effect on vasomotor symptoms.

Dietary Modifications

There is a scarcity of data on the efficacy of lifestyle strategies to alleviate VMS. The Women's Health Initiative randomized trial recruited 17,473 postmenopausal women who were randomized to a dietary intervention consisting of increasing fruit, vegetable and whole grain intake and aimed at reducing fat intake and control group. The intervention included rigorous behavioural interventions, and sessions with both certified nutritionists and registered dietitians. Results showed that substantial weight loss of 10% over a year in the treatment arm significantly eliminated or reduced VMS compared to controls [19]. An RCT compared a low fat vegan diet including nuts and avocados with a normal diet monitored by weekly group Zoom sessions. A significant decrease in VMS of 88% was found in the treatment group compared to a 34% decrease in controls. Neither seasonality nor equol production were related to the outcomes [20]. This trial included women experiencing only 2 VMS per day and its effect on women with more frequent VMS is unknown. A longitudinal cohort study of 6040 women

with a natural menopause followed at 3 yearly intervals for 9 years found that a higher consumption of fruit or a Mediterranean style diet were inversely associated with vasomotor symptoms when comparing top and bottom quartiles, whereas diets high in fat or sugar increased the risk of VMS [21]. However, an Australian cross-sectional study confirmed no relationship between Mediterranean diet and VMS [22]. Overall, data from clinical trials do not confirm the benefit of dietary modifications as an intervention to help alleviate VMS.

Paced Respiration

Paced breathing is a technique that involves consciously slowing down and controlling breathing rate, often with a focus on the length of each inhale and exhale, ideally by breathing in slowly and deeply through the nose for six to eight counts per minute and then breathing out through the mouth. Data have shown that paced respiration can lower sympathetic nervous activity and it has been suggested that a possible behavioural intervention to alleviate VMS although evidence is limited [1]. A small randomized blinded three-arm parallel-group trial found that paced respiration in participants showed similar results to the group who practiced usual breathing [23], while in a small, partially blinded trial of peri- and postmenopausal women, using a guided breathing device at least once daily to slow down their breathing rate, had a substantially less beneficial effect than a control group [24]. Paced respiration is not recommended as an effective nonhormone intervention to reduce prevalence and severity of VMS [1].

Recommendations and Key Messages

- Cognitive Behavioral Therapy (CBT) is recommended as an effective non-hormonal therapy for alleviation of bothersome VMS in both menopausal women and breast cancer survivors. ⊕⊕⊕⊕ A
- HCPs should be aware that CBT is also effective in improving mood, sleep and quality of life. ⊕⊕⊕⊕ A
- CBT is effective in different intervention modalities, offering a range of less costly interventions to help lower medical costs, and is useful for those women unable to attend therapy in person. ⊕⊕⊕◯ B
- HCPs should be aware that clinical hypnosis enhances mind and body interaction. ⊕⊕⊕⊕ A
- Clinical hypnosis is recommended as an effective therapy to reduce the frequency and severity of menopausal VMS. ⊕⊕⊕◯ B
- HCPs should be aware that studies have shown an association between weight gain, central adiposity and vasomotor symptom prevalence. ⊕⊕⊕◯ B
- HCPs should be aware that attainment of normal weight is a desirable public health outcome, and limited evidence suggests that weight loss may be recommended to alleviate VMS in some women. ⊕⊕◯◯ D
- A healthy diet is important for good health outcomes and disease prevention. ⊕⊕⊕⊕ A
- Data from clinical trials do not confirm the benefit of dietary modifications to alleviate VMS. ⊕⊕◯◯ D
- Due to a lack of evidence, paced respiration is not recommended for the alleviation of VMS. ⊕⊕◯◯ D

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24. Complementary Therapies

Acupuncture and Related Techniques

There is a reasonable body of evidence on acupuncture and related techniques. Acupuncture and related techniques are safe interventions with serious adverse events being rare. Acupuncture is also well regulated in many countries, including Western countries, and is accessible, although the cost of repeated treatments needs to be considered.

Findings concerning acupuncture and related modalities, such as acupressure and auricular acupressure, are inconsistent across studies. Acupressure could be considered for improving quality of life and menopausal symptoms [1,2]. There is insufficient evidence to recommend manual acupuncture for vasomotor symptoms [3], however, electro-acupuncture could be taken into consideration [4]. The strong evidence to recommend the use of acupuncture for menopausal symptoms, anxiety and depression, quality of life and sleep is lacking, however, some studies demonstrate its efficacy for menopausal and psychological symptoms [5,6].

Overall, there is insufficient evidence to recommend auricular acupressure for menopausal symptoms, depression, and improving sleep quality. Although some studies reported modest improvements [7,8], these were not clinically significant, and no evidence of efficacy compared with sham interventions for sleep quality was observed [7,9]. However, auricular acupressure is likely to be safe. There is insufficient evidence to recommend laser acupuncture for bone and cardiometabolic health due to evidence deriving from a single, small RCTs only. However, one small RCT reported that laser acupuncture improved lipids, blood pressure and waist circumference, and the intervention appears to have a favorable safety profile [10].

Acupuncture Combined with Chinese Herbal Medicine

Acupuncture is frequently combined with other Chinese healthcare modalities, such as Chinese herbal medicine (CHM). Women and healthcare professionals (HCPs) could consider using acupuncture along with CHM for menopausal symptoms [11]. There is insufficient evidence to recommend acupuncture and CHM for sleep quality in general, however, HCPs and women may consider this combination in women with perimenopausal insomnia [12]. There is insufficient evidence to recommend acupuncture and CHM for anxiety symptoms, but women and HCPs may consider using such a combination for depressive symptoms [13]. Its short-term use appears to be safe.

Chinese Herbal Medicine

An increasing body of evidence supports the use of CHM for the management of menopause. CHM may be considered a therapeutic option for alleviating menopausal symptoms, improving sleep quality, and regulating blood pressure. Guizhi Fuling Wan is a commonly used standardized formula and is readily available wherever CHM is dispensed. Overall, CHM may have a small effect on improving bone health (bone mineral density (BMD)) although these findings may not be clinically significant [14,15]. Standardized preparations that have been trialled for bone health include Yushen Hezhi therapy and Xianling Gubao capsule. There is insufficient evidence to recommend CHM for quality of life and lipid metabolism benefits. HCPs and women should be informed that short-term use of CHM appears to be safe. HCPs should be aware that use of CHM may be considered mainstream in some cultures and countries such as in China, Taiwan, Hong Kong, Japan and South Korea.

Herbal Medicine and Nutrient Supplements

There is now a significant body of evidence regarding the use of herbal medicines and nutrient supplements. However, most of this evidence derives from individual RCTs focusing on single interventions. Evidence from meta-analyses and/or systematic reviews is available for several substances, including black cohosh, rhubarb, sage, ginseng, curcumin, vitamin D (with or without calcium), phytoestrogens and isoflavones, probiotics, omega-3 fatty acids, vitamin E, pomegranate, and pollen extract.

Pooled herbal and nutrient supplements

Based on a number of pooled analyses, HCPs and women might consider nutrient supplements and herbal medicines (particularly plant-deriving ones) for improving vasomotor, menopausal symptoms and mood symptoms [16,17]. However, the clinical utility of these pooled analyses of heterogeneous interventions is limited, and the extent to which these findings are applicable in clinical practice remains unclear.

Black cohosh

Based on evidence from a well-conducted meta-analysis of mostly low/unclear risk of bias studies (22 RCTs, n=2310) [18], HCPs and women could consider black cohosh for managing vasomotor and menopausal symptoms. However, black cohosh should not be taken into account for managing psychological symptoms. HCPs should inform women that short-term (for 3-6 months) use of isopropanolic black cohosh extract appears to be safe with no increase in hepatotoxicity, endometrial thickness or breast imaging changes [19].

Rhubarb

HCPs and women could consider supplementation with a standardized and commercially available *Rheum rhaponticum (*rhubarb) extract (ERr 731) for management of menopausal symptoms [20], while taking into account the scarcity of evidence confirming its safety.

Sage (Salvia officinalis)

Overall, there are no indications for the use of sage in alleviating menopause symptoms. Sage should not be considered for management of hot flushes, given the limited evidence suggesting its lack of efficacy compared to placebo [21]. There is insufficient evidence to recommend sage for depressive symptoms [22].

Panax ginseng

HCPs and women could consider ginseng for improving the quality of life and vasomotor/menopausal symptoms with the majority of studies trialling Korean Red Ginseng at doses of 0.2-3g/day [23]. However, ginseng should not be offered for sexual dysfunction [23], and caution should be exercised in women with hypertension due to reports of slight increases in systolic blood pressure at 12 weeks (+1.56 mm/Hg). Recommendations on optimal type and dose of ginseng are not possible due to insufficient evidence.

Curcumin

Overall, the data related to the use of curcumin in the management of menopausal symptoms is limited. We suggest that curcumin not be considered for management of blood pressure due to limited evidence for its efficacy [24]. There was insufficient evidence for its usefulness in managing vasomotor

and menopausal symptoms and BMD. Curcumin could be considered for improving fasting blood glucose and may have an impact on some but not all lipid parameters [25]. Curcumin could be considered for improving quality of life, however, the evidence for its efficacy is very weak [26,27]. The safety profile of curcumin use remains unclear due to lack of reliable data.

Vitamin D with or without calcium

There is now a reasonable body of evidence on the role of vitamin D (with or without calcium) in the menopause. HCPs and women could consider supplementation with vitamin D 800IU and calcium 1200mg daily to reduce fracture risk (hip and all non-vertebral) in postmenopausal osteoporosis [28]. However, vitamin D and calcium is not recommended to reduce fracture risk in women without osteoporosis, particularly as long-term studies have demonstrated increase in cardiovascular disease risk.

Vitamin D could be considered for managing hyperglycemia and triglycerides, however, should not be recommended for managing other lipid parameters or blood pressure, as limited evidence suggests vitamin D may increase both systolic and diastolic blood pressure [29].

Women and HCPs should be informed that, as demonstrated in the long-term postintervention follow-up of a 7-year RCT of calcium and vitamin D, supplementation of 1000mg calcium and 400IU vitamin D daily increased the risk of cardiovascular mortality in women over 50 years [30].

Phytoestrogens and isoflavones

There is an expanding body of evidence on phytoestrogens and isoflavones. HCPs and women may consider using soy-derived isoflavones (standardized to 40-100mg of soy isoflavones) to manage hot flushes and for menopausal symptoms; however, current evidence is insufficient to support the use of red clover for these indications [17]. Additionally, there is insufficient evidence to recommend isoflavones for improving quality of life, urge incontinence symptoms, or palpitations associated with menopause.

Isoflavones are not recommended to improve bone health, as to date, published studies have demonstrated minimal differences between isoflavone users and placebo groups, which makes them unlikely to be clinically significant and the results are not consistent across sites [31,32]. The use of phytoestrogens and isoflavones does not appear to cause serious adverse events in the short term, although minor and self-resolving adverse events such as gastrointestinal discomfort may occur.

The effects of soy isoflavone on breast tissue may depend on endogenous estrogen concentrations. A French cohort study of 76,442 women reported decreased risk of estrogen-receptor (ER) positive breast cancer and increased risk of ER negative breast cancer with soy supplement use, as well as increased risks in women with a family history of breast cancer, or >5 years post menopause[33]. Dietary intake of soy foods (which is roughly 50mg/day) does not appear to be harmful and is in fact associated with a lower risk of estrogen-receptor positive breast cancer [34-35]. A meta-analysis of observational studies reported that women with breast cancer who used soy protein or soy products after diagnosis had a reduced risk of recurrence, particularly if they had ER positive breast cancer, with a dose-response analysis suggesting that the greatest risk of reduction was seen with intakes of 60mg/day or above [36]. A reduction in breast cancer specific mortality was also reported in women with ER positive breast cancer who used soy protein and products after diagnosis, but there was no difference in

mortality in women with ER negative breast cancer [36]. HCPs and women should exercise caution if there is a family history of breast cancer and in women >5 years post-menopause.

Probiotics

Although the evidence on probiotics for menopausal symptoms, QoL, and mood symptoms is promising, it is still insufficient to allow a recommendation for these indications. Additionally, we suggest that probiotics should not be recommended for management of cardiometabolic risk factors due to potential for hyperglycemia in one RCT. Other studies did not report a difference in adverse effects between groups [37].

Probiotics could be considered for improving lumbar BMD in menopausal women. A greater effect may be seen in women with osteopenia rather than osteoporosis, and with >12 months duration [37]. Most trials used a multi-strain preparation, and strains included *Lactobacillus* strains (e.g., *acidophilus, rhamnosus, reuteri, paracasei*) and *Bifidobacterium* strains, e.g., *longus.*

Omega-3 Fatty acids

Overall, due to insufficient evidence, there are no indications for the use of omega-3 fatty acids for bone health, vasomotor and mood symptoms, and lipid profiles. Particularly, they should not be offered as an alternative to MHT for bone health [38]. Omega-3 fatty acids may result in a small increase in LDL levels [39]. The use of omega-3 fatty acids appears to be safe in the short term, although increased level of blood glucose has been reported.

Vitamin E

Evidence on the clinical utility of vitamin E is inconsistent, and our recommendations are limited by the potential harm deriving from the use of vitamin E. Women and HCPs may consider vitamin E for management of vasomotor symptoms [25,40]. There is, however, insufficient evidence to enable recommending vaginal vitamin E for improving quality of life, vaginal symptoms, sexual function and insomnia [41-43]. We suggest that HCPs and women do not consider using vitamin E for the management of dyslipidemia due to inconsistent findings present in limited literature.

The systematic review of Feduniw et al. analyzes the effect of vitamin E supplementation on postmenopausal women and suggests that a high dose (>400IU/daily) of vitamin E should be avoided. However, it is worth noting that trials analyzed in that literature review mainly involved participants with chronic disease [44]. Feduniw et al. also noted that increased risk of haemorrhagic stroke with Vitamin E had been reported in men who were smokers [44].

Pomegranate (Punica granatum)

Pomegranate extract (obtained either from the fruit or seed) is thought to have antioxidant and phytoestrogenic properties [45]. HCPs and women may consider using pomegranate for hot flushes and menopausal symptoms. While pomegranate appears to have a positive effect on HDL cholesterol, current evidence does not support its efficacy in improving LDL cholesterol [45].

Pollen extract

There is insufficient evidence to recommend pollen extract for hot flushes.

Other Herbs and Nutrients

There is a large number of herbs and nutrients that have only been evaluated in a single clinical trial. Overall, the up-to-date studies provide no sufficient evidence to recommend the use of these interventions, although potential benefits have been observed.

The following nutrients and herbal products showed no significant efficacy for vasomotor or other menopausal symptoms, nor for improvements in quality of life: purified pollen extract [46], placental extract pharmacopuncture [47], *Cissus quadrangularis* [48], fermented sarco-oyster [49], propolis [50], blackcurrant [51,52], green lip mussel [53], L-leucine [54], hops extract [55,56], L-citrulline [57,58], epicatechin [59], olive leaf [60], collagen peptides [61], evening primrose oil [62], *Nigella sativa* [27,63]. Women and HCPs should be informed that subarachnoid haemorrhage was reported with placental extract pharmacopuncture although it was not assessed as being related to the intervention [47].

While preliminary findings suggest potential efficacy of certain herbal formulations, such as *Cornus mas* [64], *Ferula communis* [65], *Pimpinella* [66], rhubarb [67], *Cynanchum wilfordii* Hemsley, *Phlomis umbrosa* Turczaninow, *Angelica gigas* Nakai [68] or shatavari [69], in the management of vasomotor symptoms, the current body of evidence remains insufficient to support their clinical recommendation for this indication.

HCPs should discuss the risk of vaginal spotting with *Pimpinella*.

Several interventions have demonstrated potential benefits across a range of indications, including menopausal symptoms, quality of life, sleep quality, mood disturbances, and sexual function. These include *Ocimum basilicum* (basil leaf) [70,71], *Cinnamomum verum* (cinnamon) [72], *Cirsium japonicum* var. *maackii* (Maxim.) Matsum., *Thymus vulgaris* L. [73], fennel [62], frankincense [74], *Dracocephalum* spp. [75], *Viola odorata* [76,77], flavonol-rich cacao [78], saffron [79], costus oil massage [80], nettle cream [81], *Ferula communis* [65], *Rosa damascena* [82], chamomile vaginal gel [83], *Vitex agnus-castus* [84], green tea extract [85], *Schisandra* spp. [86], and *Tribulus terrestris* [86]. However, the current evidence base is insufficient to support their routine use in clinical practice.

Mind-Body Therapies

Traditional Chinese exercises (Tai Chi and Qi Gong)

HCPs and women may consider traditional Chinese exercises such as Tai Chi and Qi Gong for improving BMD in postmenopausal osteoporosis. The evidence is stronger for Tai Chi, however, this type of activity is not superior to other forms of moderate exercise such as walking or skipping rope, or as an adjunct to calcium and vitamin D, and differences in BMD for Tai Chi may be small [87]. Tai Chi should be practised for 6 months or more for a greater impact on bone health [87].

HCPs and women could consider traditional Chinese exercises, particularly Tai Chi and Baduanjin (the "eight-piece brocade" form of Qi Gong), for management of depressive symptoms in the peri- and post-menopause [88]. There is insufficient evidence to recommend Tai Chi for improving quality of life, sleep disturbances [89] and metabolic health (waist circumference and blood pressure) [90] in menopausal women. Although practising Qi Gong appears to bring some benefits for menopausal symptoms, psychological symptoms, quality of life, sleep, and sexual function, there is insufficient evidence to enable the recommendation of it for these indications [91-93]. HCPs and women should be informed that Tai Chi and Qi Gong appear to be safe interventions.

Yoga

Yoga may be offered as a therapeutic option for the management of menopausal symptoms [2]. In addition, it may provide benefits for sleep quality and mood disturbances [94,95], as well as contribute to improvements in certain aspects of cardiometabolic health, including body mass index (BMI), diastolic blood pressure, and selected lipid parameters [95,96]. However, current evidence does not support a beneficial effect of yoga on quality of life or vasomotor symptoms [95]. Therefore, it is not recommended that yoga be offered specifically for these indications.

Mindfulness-based interventions (MBIs)

HCPs and women may consider MBIs for management of stress, anxiety, depression and sleep disturbances during the menopausal transition and postmenopause. Although Mindfulness-Based Stress Reduction (MBSR) shows promise in the management of menopausal symptoms—as measured by the Menopause Rating Scale [2] — the current evidence is insufficient to support its recommendation for this indication. There is insufficient evidence to recommend MBSR for QoL [2]. Additionally, while the evidence on Mindfulness-Based Cognitive Therapy for QoL is promising [97], it remains insufficient to support its recommendation for this indication. We suggest that MBIs are not offered for improving sexual function due to limited evidence for its efficacy [98,99].

Other mind-body therapies

There exist several mind-body therapies, such as Emotional Freedom Technique, reiki, progressive muscle relaxation technique, that may be considered for management of menopausal symptoms. However, despite promising outcomes, the evidence remains insufficient to support their recommendation for this indication [100-102].

Other Therapies

Aromatherapy

There is insufficient evidence to recommend aromatherapy with or without massage or mindfulness-based interventions for the management of menopause symptoms. Evidence on aromatherapy (either as inhalation or ingestion of essential oils) during the menopause was limited to single, small RCTs. These reported no differences for vasomotor and menopausal symptoms, quality of life, and lipid profiles [103,104]. There were inconsistent findings regarding sleep quality, mood and sexual function improvement [98,103-105]. Noteworthily, inhalation of essential oils is unlikely to cause significant harm.

Massage and touch therapies

Women and HCPs may consider massage and touch therapies for the management of vasomotor symptoms, menopausal symptoms, quality of life, and improving sleep quality and mood symptoms. There is insufficient evidence to recommend foot reflexology as an adjunct to aerobic exercise for managing hypertension [106].

Homeopathy

Although the evidence on homeopathy for the management of menopausal symptoms appears promising [107], it is currently insufficient to support its recommendation for this indication. Additionally, there is a lack of sufficient evidence to support the use of homeopathy for improving quality of life [107].

General Practice Points

HCPs should enquire about concurrent use of complementary therapies and conventional approaches, as well as about patient preferences regarding management of the menopause. Women should be informed that regulations regarding complementary therapies vary, misinformation is common, and credible scientific information that is free of commercial interest should always be sought. HCPs should engage in respectful, patient-centered shared decision-making, considering individual values and preferences, when it comes to discussing complementary therapies. We recommend that complementary therapies, if chosen, are used as an adjunct to conventional options in the first instance. HCPs should be informed that the use of traditional medicines may be an important and well-accepted part of an individual's cultural background and should consider this when discussing the use of complementary therapies.

Recommendations and Key Messages

- HCPs should enquire about concurrent use of complementary therapies and conventional approaches, and about patient preferences with regard to management of the menopause. GPP
- Women should be informed that regulation of complementary therapies varies, misinformation is common and credible scientific information that is free of commercial interest should always be sought. GPP
- HCPs should engage in respectful, patient-centered shared decision-making, considering individual values and preferences, when it comes to discussing complementary therapies. GPP
- We suggest that complementary therapies, if chosen, are used as an adjunct to conventional options in the first instance. GPP
- HCPs should be informed that the use of traditional medicines may be an important and well-accepted part of an individual's cultural background and should consider this when discussing the use of complementary therapies. GPP
- Women and HCPs could consider electro-acupuncture for VMS but there is insufficient evidence to recommend manual acupuncture. ⊕⊕◯◯ C
- There is insufficient evidence to recommend the use of acupuncture for menopausal symptoms, anxiety and depression, quality of life and sleep; however, some studies demonstrate efficacy for menopausal symptoms and psychological symptoms, and acupuncture is likely to be safe. ⊕⊕◯◯ C
- There is insufficient evidence to recommend acupuncture + CHM for sleep quality in general; however, HCPs and women may consider the combination in women with perimenopausal insomnia. ⊕⊕⊕◯ C
- CHM could be considered for improving menopausal symptoms, sleep quality and blood pressure. ⊕⊕⊕◯ C
- HCPs and women should be informed that short-term use of CHM (up to 1 year) appears to be safe. ⊕⊕⊕◯ A
- HCPs and women could consider black cohosh for managing vasomotor and menopausal symptoms; however, black cohosh should not be considered for managing psychological symptoms. ⊕⊕⊕◯ C
- HCPs should inform women that short-term use (3-6 months) of isopropanolic black cohosh extract appears to be safe. ⊕⊕◯◯ A
- HCPs and women could consider supplementation with 1200 mg calcium and 800 IU vitamin D daily to reduce fracture risk in postmenopausal osteoporosis. However, routine calcium and vitamin D supplementation is not recommended for fracture prevention in women without osteoporosis or deficiency states. HCPs should discuss the potential for increase in

cardiovascular risk, which has been reported in some long-term studies, when recommending calcium and vitamin D for other indications. ⊕⊕⊕◯ A

- HCPs and women could consider using soy-derived isoflavones to manage hot flushes and for menopausal symptoms; however, there is insufficient evidence to recommend red clover for reducing hot flush frequency. ⊕⊕◯◯ C
- While dietary intake of soy foods is unlikely to be harmful, HCPs and women should exercise caution with soy isoflavone supplementation if there is a family history of breast cancer or past history of estrogen receptor-negative breast cancer. ⊕⊕◯◯ B
- Probiotics could be considered for improving lumbar BMD in menopausal women. A greater effect may be seen in women with osteopenia rather than osteoporosis, and with >12 months duration. ⊕⊕◯◯ C
- HCPs and women could consider traditional Chinese exercises such as Tai Chi and Qi Gong for improving BMD in postmenopausal osteoporosis. The evidence is stronger for Tai Chi; however, Tai Chi is not superior to other forms of moderate exercise such as walking or the skipping rope, or as an adjunct to calcium and vitamin D, and differences in BMD for Tai Chi may be small. Tai Chi should be practised for 6 months or more for a greater impact on bone health. ⊕⊕◯◯ C
- HCPs and women could consider traditional Chinese exercises, particularly Tai Chi and Baduanjin, for management of depressive symptoms in the perimenopause and postmenopause. ⊕⊕◯◯ C
- Yoga can be offered to women for management of menopausal symptoms and could be considered for other benefits including sleep and mood symptoms, and for improving some but not all aspects of cardiometabolic health (including BMI, diastolic blood pressure and some lipid parameters). ⊕⊕◯◯ C
- HCPs and women could consider mindfulness-based interventions (MBIs) for management of stress, anxiety, depression and sleep disturbances during the menopausal transition and postmenopause. ⊕⊕◯◯ C
- Women and HCPs could consider massage and touch therapies for the management of VMS, menopausal symptoms, quality of life, and improving sleep quality and mood symptoms. ⊕⊕◯◯ C
- Evidence ratings for other interventions, including a large number of herbs and nutrients, are very low. Overall, evidence is insufficient to recommend the use of these interventions. GPP

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25. Compounded 'Bioidentical' or 'Natural' Hormones

Although pharmaceutical compounding of medicines by pharmacists has existed since the discovery of a mortar and pestle, the explosion in compounded hormone therapy occurred largely as a response to the Women's Health Initiative (WHI) publication on adverse results of estrogen and progestin therapy [1]. To distinguish the compounded products from those used in the WHI study, compounders settled on the term 'bioidentical'. Pharmaceutical companies worldwide also produce menopausal hormone therapy (MHT) containing hormones identical in structure to human hormones. These may be described / referred to as 'body identical' to differentiate them from the untested compounded alternatives that do not follow the same strict regulatory pathways applied to prescribed medicines [2]. In some cases, pharmaceutical companies will describe these regulated products as 'bioidentical' which may add to confusion amongst consumers.

In this discussion, we will refer to compounded unregulated bioidentical hormone therapy products as "cBHT" and the regulated products produced by pharmaceutical companies as "MHT".

The term 'bioidentical', in the context of MHT, means having the same molecular and chemical structure as the sex steroid hormones produced by and circulating throughout the body [3,4]. Bioidentical hormone therapy (BHT) is not a scientific term. It is a term used as a marketing tool, implying that the product is natural or safer, and as a technical term to suggest that the chemical structure is identical to endogenous hormones including estradiol, estrone, estriol, progesterone, testosterone and DHEA. The deception lies in the fact that 'bioidentical' hormones must be synthesised biochemically from plant sources. Compounded BHT does not follow the same regulatory pathways as government approved MHT [3,5,6], and is not approved by government bodies to treat menopausal symptoms. This means that cBHT does not have to undergo the same rigorous scrutiny in terms of manufacturing standards, quality control and oversight as pharmaceutical-grade registered products [7,8].

Different countries will implement their own guidelines regarding the manufacturing and testing of various medications which include extensive clinical trial research, marketing and ongoing oversight to ensure patient safety [9]. Unlike cBHT, pharmaceutical grade products have been meticulously checked for quality, purity and efficacy. They are distributed with applicable package inserts that have safety warnings and describe possible adverse side effects of MHT. They also include extensive evidence-based information from peer reviewed data including reliable double-blind randomized placebo controlled trials (RCTs). These inserts are not distributed with cBHT as there are no peer reviewed scientific data to confirm the unproven marketing fiction that cBHT is more 'natural' or safer, and that women using it will have a lower risk of side effects than MHT [4,6]. RCTs of cBHT are lacking, and there is very limited evidence of the increased risk of cardiovascular disease, breast and endometrial cancer, and other adverse effects or benefits of cBHT [10], however, case reports confirming the association of endometrial hyperplasia and cBHT do exist [11].

Advocates of cBHT often claim, incorrectly, that their preparations are made to meet a woman's individual needs, and will order salivary, urine or especially / preferably blood serum assays to determine a woman's hormone levels [12]. Combinations of cBHT are then prescribed based on what the healthcare provider has decided is the appropriate hormone level for that individual woman.

However, neither optimal levels of estradiol and other sex steroid hormones in midlife/menopausal women, nor ideal doses of hormones to treat menopausal symptoms have been scientifically established [4,7].

The use of these assays is unreliable because hormone levels fluctuate due to several factors, including differences in absorption and variations in background endogenous hormone production from the ovaries of perimenopausal women [7,9]. Further, hormone assays on saliva and urine have not been adequately validated for sex steroids. The testing of a particular hormone level is not recommended in midlife women unless it is to test for a specific reason, such as infertility, the assessment of adverse effects, inadequate response to treatment, or the inability of a woman to determine whether she is menopausal when she does not have a uterus and her menopause status cannot be determined by her bleeding pattern [13].

Compounded bioidentical hormone preparations are not entirely 'natural' in their content. The primary sex steroid hormones that are found in both cBHT and MHT are plant-based and come from the natural world. They are both synthesized in laboratories following the same procedure [4]. Both MHT and cBHT are easily accessible [6], although cBHT is often more expensive and not available in public healthcare clinics. Thus, women may be confused about which hormone therapy to use since the sex steroid hormones in cBHT are also found in MHT. However, there are serious safety concerns about cBHT because it is not government approved and its quality is inconsistent. In addition, there may be concerns related to impurities, efficacy, and over- and underdosing of specific hormones, as individual batches can vary [7,14,15]. Estrogen levels may be unnecessarily high, and progesterone levels may be too low to fully protect against endometrial hyperplasia and cancer. cBHT preparations often include estriol which is not present in approved systemic MHT formulations and has not been rigorously tested for efficacy and safety in RCTs. In addition, many such compounded products deliver progesterone transdermally in cream or gel preparations. The absorption of progesterone through the skin is variable with fluctuating tissue availability and, as a result, may not provide sufficient endometrial protection [16]. Although cBHT may be prescribed for women allergic to specific components of MHT, there is limited data defining the types of allergies that may occur in response to MHT [5]. Major menopause societies as well as scientific, clinical and regulatory bodies in women's health advise against the use of these products, and prescribing such products exposes healthcare providers to potential medicolegal risks [7,9].

Recommendations and Key Messages

- Prescribing of Compounded Bioidentical Hormone Therapy (cBHT) is not recommended due to safety and efficacy concerns, including lack of quality control and rigorous regulatory oversight, and absence of scientific evidence of safety, purity and efficacy. ⊕⊕⊕◯ A
- The use of blood serum assays or salivary hormone levels to prescribe the appropriate dose of cBHT is not recommended by major menopause societies. ⊕⊕⊕⊕ A
- Women should be informed that cBHT is not standardised and does not undergo the same strict regulatory processes as is the case for MHT. ⊕⊕⊕◯ A
- Women should be informed that unlike cBHT, MHT is strictly regulated and distributed with relevant package inserts and safety warnings. ⊕⊕⊕⊕ A
- Women requesting cBHT should be informed about safety issues, and encouraged to use or switch to MHT which is stringently tested for strength, purity and quality. ⊕⊕⊕◯ A
- Women should be informed that MHT is available in a wide range of doses and delivery methods, which facilitates individualization of therapy, allowing HCPs to tailor MHT regimens for individuals. ⊕⊕⊕⊕ A

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26. Emerging Insights, Therapies and Technologies in Menopause

In this section, we examine emerging insights, therapies and technologies in menopause in the last 5 years that could potentially improve the care for the midlife woman. Below, we review emerging technologies and science to highlight recent studies and innovations in menopause research. The IMS does not endorse these interventions given the preliminary nature of the science but highlights them to represent the future of research in select areas.

Emerging Insights

Insights into metabolic changes

In a small (n=9) randomized crossover study, shortened sleep duration blunted adrenergic stimulation of lipolysis and hence may contribute to gain in adiposity in post-menopausal women [1]. Future studies could validate this and lead to appropriate lifestyle interventions for menopausal women.

Understanding Symptom subtypes for individualized care

Four symptom subtypes were identified in a cross-sectional study in China: "severe symptoms'' (14.9%), ''dominant sleep-emotion symptoms'' (31.4%), ''physical/mental exhaustion symptoms'' (32.5%), and ''no symptoms'' (21.2%) [2]. Understanding the subtypes would allow more individualized approach to the treatment of menopausal symptoms. This study adds on to previous longitudinal studies looking at symptom clustering across the menopausal transition [3].

Menopausal scales

The COMMA consortium evaluated scales used to assess vasomotor and genitourinary symptoms [4,5] and provides recommendations regarding which tools to use for particular concerns, for example, the Hot Flash Related Daily Interference Scale was recommended for measuring the domain of distress, bother, or interference of vasomotor symptoms and the impact on sleep [4].

Several new scales have been developed for use in menopausal women. These include:

1. The Korean Menopause Emotional Symptom Questionnaire for screening for and measuring emotional symptoms in menopausal women in Korea [6].
2. Menopause Transition Scale. A validated patient-centric scale to measure physiological and emotional symptoms of patients in the transition through the various stages of menopause [7].

Lifestyle (diet and exercise)

In an RCT (n=84), low-fat, plant-based diet coupled with daily consumption of 86g of soybeans over 12 weeks led to significant reduction of moderate to severe vasomotor symptoms, weight loss, improvement in physical, psychosocial, and sexual domains in the intervention group [8]. In a secondary analysis, reduction in animal products and vegetable oil in diet was shown to significantly reduce menopausal symptoms [9]. Microbiome after 12 weeks showed changes in the relative abundance of *Porphyromonas*, *Prevotella corporis*, and *Clostridium asparagiforme* and these were associated with the reduction in severe hot flushes in the intervention group [10]. The limitation of the study was that it only evaluated the microbiome in the intervention arm and not the control arm.

In another sub-analysis, reduction in dietary advanced glycation end-products led to significant reduction in hot flushes [11]. The significance of dietary impact on gut microbiome was shown in

another research study where there was no difference in the microbiome in women based on the menopausal stage but was influenced by dietary habits [12].

In a cross-sectional observational study (n=59) comparing young women ages 19-23 years to perimenopausal women ages 45-55 years, physical activity was shown to alter gut microbiome. It was noted that perimenopausal women had lower level of daily physical activity even prior to measurable changes in body fat distribution and alterations in the gut microbiota [13]. *Sphingomonas* was significantly correlated with daily physical activity indicators, which might serve as a useful indicator of the level of physical activity.

A study examining salivary microbiome found no significant differences in the flora of the oral cavity between young women and menopausal women [14]. Future studies should examine both the salivary microbiome and gut microbiome to understand their association with menopausal status.

It appears that an appropriate diet coupled with physical activity can alter microbiome, which could ultimately improve menopausal symptoms experienced by the midlife woman.

Emerging Therapies

Cognitive Training Programs/Psychotherapy Programs

A program developed in Korea to enhance cognitive reserve was studied in menopausal women with subjective cognitive decline. After 8 weeks, the intervention group showed significant improvement in overall cognitive function, memory, attention and language function compared to the control group [15].

In a RCT conducted in Iran, counseling based on Acceptance and Commitment Therapy (ACT)—a recent approach in psychotherapy—was evaluated in a cohort of 86 women. After 8 sessions, intervention with ACT resulted in significant improvements in the mood of menopausal women, particularly in reducing the levels of anxiety, depression and stress [16].

New medical therapy – Estetrol (E4)

In a presentation at the annual meeting of the North American Menopause Society in 2022, estetrol (E4), a natural estrogen produced by the human fetal liver and behaving like a native estrogen with selective tissue activity, with little impact on breast tissue, was studied in 2 phase 3 two placebo-controlled, double-blind, multicenter, randomized trials. E4 combined with progesterone for endometrial safety was found to significantly reduce frequency and severity of hot flushes, at week 4 and week 12. There was also a positive effect on the quality of life at week 12 [17].

Another analysis presented at the 2024 Menopause Society Annual Meeting, examined the metabolic effect of E4. According to the presented material, 12-week treatment with E4 15 mg and E4 20 mg appeared to significantly increase in HDL-C and decrease in total C/HDL-C ratio, LDL-C and lipoprotein (a) as well as reduce fasting blood glucose and HbA1C [18]. The 52 week endpoint also showed a significant improvement in health-related quality of life as well as symptoms in another presentation at the same meeting [19].

Emerging Technologies

Digital Health

Digital health in menopause management uses technologies like apps, telemedicine, wearables and AI, to support women through menopause by enabling symptom tracking, personalised care, education and remote support for more accessible and patient-centred management.

I. Devices

a. Detecting hot flushes

Multi-sensors detection of hot flushes has been developed. This included combining consumer grade wrist-based wearable sensors (photoplethysmography, motion, temperature and galvanic skin response) with sternal skin conductance [20,21].

b. Insights into menopausal health

Wearable ring device was used in a study to show that sleep quality declined rapidly for women after menopause, in contrast to men, who experienced a more gradual change over time. [22].

Another study analyzing the use of a wearable ring showed that temperature changes across the menstrual cycle are similar between menopausal and young women. However, the mean temperature of menopausal women is higher than of young women [23].

A novel device to detect exhaled CO2 has shown the variation in CO2 levels in different phases of the menstrual cycle. Additionally, the device revealed that menopausal women not receiving menopausal hormone therapy (MHT) had higher exhaled CO2 levels compared to those undergoing MHT [24]. This modality offers a way to examine the metabolic changes in the menopausal women.

c. Device to reduce hot flushes

Wrist-worn warming and cooling device has been shown in 2 studies to improve sleep and comfort in menopausal women and breast cancer survivors experiencing hot flushes [25,26].

II. Mobile APPs

a. Apps for understanding menopausal symptoms

An online survey on menopausal women evaluating their experiences in using web-based or mobile app-based programs for mental health symptoms related to menopause, revealed that the topics of most interest were those related to menopause symptoms characteristics and treatment options [27]. The most desired app feature was psycho-education, followed by symptoms tracking and self-help tips. Credibility of the apps being developed by psychiatrists or reputable academic institutions is the key factor driving the intention to use an app or web-based program. Some barriers encountered by the app users included discomfort in an app assessing one's mental health and doubts about the ability to understand complex mental health issues.

The range of currently available apps used to monitor menopausal symptoms is quite vast. Data collected from Strava and MenoLife applications were used to better understand menopausal status and manage the menopause related symptoms [28,29]. As more women use consumer wearables and health-related apps, there is a growing opportunity to reach a broader segment of the female population for participation in future studies like the Apple Women's Health Study [30].

b. Apps that improve menopausal symptoms

Apps have been developed and studied for improving the management of menopausal symptoms. For example, the Health & Her app provides menopausal women with information related to menopausal symptoms triggers and menstrual periods monitoring, as well as encourages engagement in digital activities to promote well-being. The study analyzing the use of this application demonstrated a significant reduction in symptoms after 2 months, especially with constant, weekly engagement [31]. A mobile app that delivers audio-recorded hypnotherapy has shown promising results with 76% of women reporting at least 50% reduction in daily hot flushes and night sweats [32]. In study, a menopause self-care app has demonstrated its usefulness in reducing menopausal symptoms and improving marital relationship (intervention group) compared to usual care (control group) after 8 weeks [33].

A small Korean study (n=48) has analyzed the usefulness of Menopause Assistant Manager, a menopause app that includes personalized information related to menopause, exercise coaching, and management of appointments and medications. The comparison of intervention group with the to waitlist control group demonstrated a significant improvement in the physical and environmental quality of life among the app users. Anxiety and somatic symptoms were also significantly reduced after 8 weeks of intervention [34].

A UK study has presented promising results regarding an employer-provided app (Peppy Health menopause application) that included evidence-based menopause content, activities provided by expert menopause practitioners, video consults, and text-based consultations and conversations with personalised support for menopausal symptoms management. It was demonstrated that the use of this application significantly improved menopausal symptoms and reduced work impairment after 90 days of its usage for perimenopausal and menopausal women [35].

Apps that provide effective interventions have potential to reduce the inequality to healthcare access and allow more women to receive effective treatment.

c. Quality of Apps

In an analysis of 14 menopause Femtech apps available in European Union on Google Play, it was found that only 21% of those apps met more than 50% of the criteria required by General Data Protection Regulation (GDPR) for data privacy and security sufficiency [36]. While several studies in the previous sections showed the effectiveness of app-based interventions, healthcare professionals (HCPs) need to be aware of the regulatory requirements when rolling out digital interventions.

III. Telehealth

In a prospective, observational study of a video telehealth service for postmenopausal cancer survivors, satisfaction, standard of care, consultation duration and patient rapport achieved positive feedback from clinicians, while technical difficulties and finding the platform distracting were the key factors for negative feedback [37]. For patients, time and cost saving as well as convenience were the key points for positive feedback. Most patients found the platform easy to use with no technical difficulties and the majority were willing to use the service again.

A qualitative study has analyzed the menopause experiences of female nurses (n=48) aged 45-55 from six different countries in their workplace. The shared experiences helped to identify four major menopause-related themes: managing symptoms in the workplace, recognition in the workplace,

menopause interventions and expectations versus the invisible reality [38]. These themes uncovered actionable insights for use in digital health implementation.

In a study involving women with early menopause (EM) (n=150), participants completed surveys before and one month after engaging with digital educational resources, including audio and video clips on EM, information about healthcare providers, a question prompt list, resource links, and a directory of services. One month after exposure to these materials, there was a significant increase in knowledge about the benefits of menopause hormone therapy, along with improved scores on questions assessing understanding of early menopause [39].

A Saudi Arabian study (n=80), evaluating the efficacy of an Internet-based, cognitive behavioural therapy (CBT) program on sleeping difficulties in menopausal women, demonstrated its effectiveness in improving various sleep parameters, particularly in sleep quality, its duration and efficiency [40].

Machine Learning/Artificial Intelligence

Machine learning (ML) and artificial intelligence (AI) has enabled identification of new associations and factors influencing menopause and its related issues. This area will certainly grow in prominence with the advent of more powerful AI software coupled with faster cloud computing capabilities. Below are the studies that have emerged in the last 5 years.

I. Case definition

Natural Language Processing (NLP), ML and algorithm-based techniques trained on electronic medical records have enhanced the classification of menopausal status, thereby improving data analysis related to midlife women's health and supporting more informed clinical care [41-43].

II. Studying factors affecting menopausal symptoms

In a recent study on machine learning and menopause related depression ML techniques were utilised to analyze the relationship between psychological, behavioural and personality factors in menopausal women [44]. ML was also used to discover the factors affecting vasomotor symptoms. In a Korean study, several VMS associated factors, such as menopause age, thyroid-stimulating hormone, and monocyte, triglyceride, gamma glutamyl transferase, were evaluated. The study confirmed that ML can provide an important decision support system for the prediction of VMS [45].

An ML-based network analysis combined with the Walktrap algorithm were used to study the data from Study of Women's Health Across the Nation (SWAN, Visit 5) [46]. The collected data revealed that symptom clusters experienced by perimenopausal and postmenopausal women with metabolic syndrome were different from those without metabolic syndrome.

Mixed method study using natural language processing to analyze text from an online community and semi-structured qualitative interviews was used to elicit patient's experience and management of vasomotor symptoms [47]. Coping strategies included medication and lifestyle modification. Majority of the women felt that their HCP was unsympathetic or unhelpful.

ML models were also used to identify the factors that were related to severe subjective cognitive decline in nurses during the menopause transition. Key factors included severity of menopausal symptoms namely frequent or severe hot flushes, mood swings and sleep disturbances [48].

Predicting Menopausal Age and POI

I. Machine learning/AI

Data mining from National Health and Nutrition Examination Survey (NHANES) 2013-2014 revealed factors such as early menarche and BMI to be associated with age of menopause [49]. Other factors such vitamin B12, vitamin D and sex-hormone binding globulin (SHBG) were important factors in the model developed and would require further investigations in future studies.

A model for predicting natural onset of menopause was developed by Kastrati et al (2024) based on a Swiss cohort and externally validated on a Dutch cohort [50]. The model tested several predictors, such as age, alcohol consumption, smoking status, education level, and systolic blood pressure - all of which could potentially be used with calibration in various populations to improve care for women.

In a nationwide, multi-centre study involving 6 cities in China, Ding et al (2023) found that using Machine Learning methods combining multi-features were reliable in assessing and quantifying ovarian reserve [51].

II. Genetics

An increasing number of studies are using genome-wide association study (GWAS) meta-analysis with databases such as the UK Biobank, BioBank Japan Project, Reproductive Genetics Consortium, and the 1000 Genomes Project, across multiple countries, to identify new genetic variants and loci linked to premature ovarian insufficiency and early menopause [52-55].

In a 2022 study by Magnus et al the UK Biobank cohort was used to find that a genetic predisposition to younger age at natural menopause was associated with lower bone-mineral density, higher risk of breast cancer and higher HbA1C which was replicated in another independent cohort [56].

Discovery of new variants associated with POI in women has also been accelerated by sequencing in cases and comparing to existing databases, including genes belonging to DNA repair, meiosis and mitosis, suggesting potential implications for cancer susceptibility [57-59]. A combination of genetic sequencing techniques has also led to understanding of the mechanism of POI and association with mitochondrial metabolic dysfunction, oxidative stress and inflammatory markers [60-62].

Alternative Therapies

Complementary and Alternative Medicine (CAM)

A phase 1b/2a double-blinded RCT (n=46) on a nutraceutical comprising of three phytoestrogens: genistein, daidzein, and S-equol showed significant reduction in hot flushes for the 50mg preparation compared to placebo over 12 weeks [63]. We are awaiting the results from the larger phase 2 trial to see if the results are consistent.

A well designed, double-blinded placebo RCT, where homeopathic treatment consisting of individualized homeopathic medicines in the intervention arm did not show significant improvement compared to placebo [64].

Acupuncture appears to be promising as an alternative for treating women with menopausal symptoms. In an open-label, randomized, active-controlled trial (n=80), twice-weekly acupuncture for 2 months was compared to menopausal hormone therapy (cyclical 2 mg estradiol valerate with 1 mg

cyproterone acetate). Acupuncture was found to significantly reduce menopausal symptoms and notably increase serum estrogen (estradiol, E2) and 5-hydroxytryptamine levels [65].

Ovarian Platelet-Rich Plasma (PRP) Injections

PRP has emerged to be promising in restoring ovarian function in women experiencing POI or early menopause. In a retrospective observational study (n=469) in Greece, FSH levels were noted to significantly reduce at 3 and 4 months after the PRP intraovarian injections [66].

Another study in Han Chinese (n=12) showed that PRP was able to restore ovarian function in early menopausal women [67].

A recent systematic review and meta-analysis revealed that intraovarian injection of PRP may improve ovarian reserve of women with poor ovarian reserve (POR) and POI. However, the studies were "before and after trials", except for one study [68]. While PRP appears to improve ovarian reserve in women with POR and POI, more properly designed RCTs need to be conducted for such an intervention to be recommended. In fact, one of the RCTs discussed in the review showed that the clinical pregnancy rate was inferior in those who received PRP compared to those in the control arm who did not receive PRP [69].

Recommendations and Key Messages

- Digital health solutions have the potential to improve access to care for women with menopausal symptoms. ⊕⊕◯◯ C
- Machine Learning and Artificial Intelligence (AI) have increased the speed of discovery of genetic and metabolic pathways that cause POI, with potential development of diagnostic and prognostic kits as well as possible interventions. ⊕⊕⊕◯ B
- Changes in the microbiome may mediate reductions in menopausal symptoms associated with lifestyle, diet and activity changes. ⊕⊕◯◯ C
- Newer interventions for menopausal symptoms in the pipeline include medical therapies such as estetrol as well as novel device-based cooling. ⊕◯◯◯ D
- Development of newer scales for menopause which are population appropriate, accompanied with the segmentation of menopausal symptom subtypes, allow for individualization of care for better outcomes. ⊕⊕◯◯ C

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Expert Reviews and Recommendations/Key Messages of Controversial Topics

The recommendations and key messages in the next three sections (27-29) were derived from narrative reviews written by our experts and could not be based on systematic reviews of the scientific literature due to the nature of the topics.

27. Influence of the Media

The media, whether mass or social, is driven by news. Not all events will be news, and news will only be considered news if reporters report and editors agree to publish. Features, which make up some half of today's editorial output, provide background to the news along with expert comment, while social media mainly offers comment, usually of a personal nature, but is used occasionally to release news.

In medicine, news coverage has traditionally been driven by press releases. However, major publishers—primarily in the UK and US, with large circulations and substantial budgets—have occasionally conducted independent investigations, leading to groundbreaking revelations such as those involving thalidomide, MMR vaccines, and breast implants. While Watergate changed the rules of general news reporting, from quiescent to confrontational, medical news remained subject to its traditional leads - from the learned journals, the drugs industry and the healthcare professions.

The first major menopause story to reach the front pages - and probably the first time menopause received widespread media attention - was the publication of the Women's Health Initiative (WHI) trial findings in 2002. Driven by a press release and press conference, the story was presented in a deliberately alarming way, with press materials written in an unrestrained, sensational tone intended to provoke strong public reaction:: "a major study (…) stopped because of health safety concerns (…) 16,608 menopausal women (…) stop prescribing estrogen plus progestin (…)" (Figure 1). The headline to that press release was breast cancer, even though cardiovascular disease was the study's original aim [1]. As a result, the following morning's reports were not unpredictable. "Alarm over HRT cancer risk", headlined the *Sydney Morning Herald,* with similar scare stories throughout the world. That indeed was 21st century news: alarming, terrifying and controversial. And just one year later, to add drama to drama, the *Lancet*'s press release for the Million Women Study reported "Substantial increase in breast cancer risk from combination hormone replacement therapy" (Figure 2).

The fallout from the WHI was well documented, and there were many reports in the media of women denied their MHT by doctors and health ministries. But against this background of public frustration and continuing symptoms, menopause remained on the inside pages and never really made big news again - until the WHI's "secondary" analysis of 2007 and the mitigating effects of patient age, which revised the risk estimates for coronary heart disease (Figure 3).

It was during this time when most journals, professional associations and governments systematically rejected MHT under the dark cloud of "harm" that the media rallied to stand up for its viewers and readers, adopting a theme of self-help and clear answers amid the MHT confusion.

It was thus a time for the experts to step forward and offer their help and explanation and stand with the media on the side of women. It is this formal neglect of women, an apparent disregard for symptoms (and their relief), which forms a strong thread of the menopause narrative in the media today. *The Lancet*'s recent four-part series on menopause announced that "almost 1 billion women worldwide are postmenopausal" while advocating a model of "empowerment" for managing this huge section of the population [2]. As defined by *The Lancet*, empowerment - an "active process of gaining knowledge, confidence, and self-determination to self-manage health" - lay behind much of the expert menopause comment of the past decade, and in the many pages of explanation, advice and personal experience recorded in the media.

But because so many women felt dismissed and ignored in the post-WHI fallout - and because menopause was now happening to a different generation of women - much of the media coverage in this latest menopause moment is reported as a response to campaigns, to single-issue champions, to one advocate's position or another. If the menopause was medicalised in the 1990s and 2000s (estrogen for all, estrogen for no-one) it surely became politicised in the 2020s. Recent news coverage has reported calls for better menopause recognition in the workplace, more sensitive prescription of MHT by the medical profession, the inclusion of "menopause" in government health agendas, themes acknowledged in the IMS white paper in 2024 [3].

Today, the press is no longer the leading distributor of news but has lost ground to digital and social media. In the USA the print circulations of the *Wall Street Journal* and *New York Times* fell by 14% and 13% respectively in the 12 months to 2023. In Britain daily circulation of *The Sun* newspaper fell from more than 3.5 million in 2000 to an estimated 700,000 in 2024. The decline in print was balanced by a rapid upturn in how people access news via mobile technology and social media platforms. A survey of "news consumption" in the UK by its watchdog OFCOM found that a declining 70% of adults get their news from television, an increasing 70% from online sources, 52% from social media, 40% from radio, and a rapidly declining 34% from newspapers.

But along with the upturn in rolling news, expert comment and citizen journalism, there has been a downside too. Trust in the media has reached an all-time low, with journalists now consistently ranked alongside politicians, advertising executives and estate agents in every veracity index published. No wonder nurses and doctors are read as more reliable health commentators than journalists!

Most alarming is the rise of deliberate or ill-informed misinformation online. According to a recent report in *Nature*, with more than 60% of the world's population now online, "false and misleading information is spreading more easily than ever" - resulting in serious consequences such as the rise in vaccine hesitancy [4]. The menopause is no stranger to this online explosion. In a study on the use of Twitter to communicate about menopause, Hunter et al. reported that globally "there were 314,974 communications about menopause on the social media platform Twitter between 2014 and 2022", with an annual average of approximately 35,000 [5].

The Influence of Social Media

In the age of social media everyone can be a publisher and anyone can have influence. Social media is now a major source of information and news, with 5.24 billion social media users globally (63.9% of the population). The typical social media user actively uses or visits an average of 6.8 different social platforms each month and spends an average of 2 hours 21 minutes per day using them. YouTube, WhatsApp, Facebook, Instagram, TikTok and WeChat are the top six most-used social media platforms, each boasting more than one billion active users.

Last year an editorial in *Maturitas* described social media in the menopause as a "two-way street", a force "for good or ill" [6]. Among the former were "building community" (helping to normalise this phase of life), "activism" and "education" (for the public and health professionals). But among the downsides were "confusion" and "misinformation" (either unintentional or for commercial gain). One cited paper reported that 16% of Instagram posts with *#menopause* were advertising services or products.

The explosion of information-sharing over the past five years, accelerated by social media, has raised awareness of menopause and its treatments in a short space of time. Google searches on menopause doubled between 2020 and 2025. The media-literate and digital native women now entering midlife/perimenopause are comfortable with and capable of seeking communities and sharing information with these platforms. This means much-needed fellowship, advocacy and support for women in a life stage that had been notably underserved in the past.

Menopause content on social media varies widely in quality and accuracy. It ranges from the personal experience of users to the overt selling of products, while some experts in the field have also been able to use social media as a platform to educate women and share information. However, many organisations have recognized menopause as a commercial opportunity. Products and services aimed at menopausal women have expanded, with marketing claims on social media not always consistent with current evidence. For example, the prescribing of testosterone for midlife women has recently been described as “out of control” by one UK newspaper, its surge in attraction attributed to “testosterone evangelists” on social media. But with transparency rules on advertising content varying around the world, such social media marketing messages are not always clearly indicated. This rarely serves a global audience well and can cause confusion.

Adding to the confusion is the perception on social media that experts are “arguing” about menopause. At a time of increasing political polarisation, exacerbated by the function of algorithms to engage users for as long as possible, the varied treatment approaches, interpretations of evidence and clinical opinions – often from practitioners in different countries - are presented as controversies. In the absence of consistent, impartial worldwide opinion, the information gap is commonly filled by individuals and groups with their own perspectives, but with various levels of accuracy and usefulness. The recent announcement by the US FDA of the changes to “black box” warnings on hormone medications in that country is an example of this in action. Some online advocates heralded the decision as an unequivocal win for women’s health, which would increase women’s lifespans and protect them from heart disease and dementia. When experts and researchers specialising in women’s health spoke out to correct some of the misinformation, they added scientific nuance to the discourse, emphasising the importance of individualized care, evidence gaps and misalignment with medical guidelines in the announcement and subsequent coverage. For women consuming the content, though, the result may be confusion.

And of course, lurking behind the misinformation is the spectre of artificial intelligence, already rampant in business, finance and healthcare (in its pathways to diagnosis and prognosis) and now stepping into publishing and the media. AI-generated headlines and captions are now common, and there is cause for concern about news sources. A study reported in 2023 concluded that “ChatGPT writes believable scientific abstracts, though with completely generated data”, while some journals have even challenged ChatGPT to write “test” editorials for analysis, and found the give-aways not easy to spot [7]. There are now products available simply to help with scientific writing, dedicated to nothing more than producing a paper ready for submission.

Recommendations and Key Messages

- There is a clear need for a broader understanding among women and media practitioners of how science works and how guidelines are formulated. However, recommendations about using the media are not easy to make, nor clearly supported by unequivocal evidence. Unlike the way in which guidelines are developed, a thorough literature search will not reveal a catalog of data from which recommendations might be systematically derived. In the case of the media, the best evidence has come from experience, both from the way in which menopause has been represented historically in the media and from our own place within it. Such recommendations thus defy grading for level of evidence, but they are based on how the media works and how menopause has, in the past and the present, claimed its place within it. KM
- It is also clear that science reporting is not easy, with roadblocks on the road to a clear story noted as medical terminology, data-loaded research, uncooperative sources, conflicts of interest, and elusive human interest in a research paper. These problems are compounded by fewer trained journalists than ever before, with many today assigned to stories in which they have no special interest and who have varying levels of scientific literacy, like their audiences [8]. But they too must translate a scientific text into a narrative understood by their readers. So, it is the responsibility of everyone, not the media alone, to ensure that the voice of authority - in a clinical paper, in guidelines, in official announcements - is expressed in clear language amenable to the public. This is already starting to happen, evident in patient summaries in some journals and guidelines and in press releases - for example in the recently updated European Society of Human Reproduction and Embryology (ESHRE) guidelines on POI (www.eshre.eu/Guidelines-and-Legal/Guidelines/Premature-ovarian-insufficiency). KM

- *The Lancet*'s recent series on menopause made a plea for "impartial information", which puts demands not just on the source of that information but also on its recipient. Biases may be commercial or ideological, but it will be useful if readers can identify the source of the information and make a value judgement on its worth and independence. KM

- To this extent, expert individuals and organisations should be encouraged to embrace social media to express a message which is clear and consistent. However, whether written or presented, the message should have a voice of authority and confidence, thereby offering a reassuring reference point for readers. KM

- Press releases continue to be the main source of medical news, and organisations with developments of public health interest in menopause should be encouraged to make greater use of them. Distribution need no longer be difficult; EurekAlert, for example, a web portal run by the American Academy for the Advancement of Science, is today's universal repository for embargoed news from the journals and universities. This offers a direct line to accredited science journalists throughout the world for a clear and accurate message. KM

Figure 1: The press release from the WHI trial, with a warning of breast cancer risk, was issued jointly by its sponsors, the National Heart, Lung and Blood Institute, and its publisher, JAMA.

SPECIAL EMBARGO FOR RELEASE: 8:30 A.M. (CT) TUESDAY, JULY 9, 2002

News Conference
Hormone Therapy Study Stopped Due to Increased Breast Cancer Risk
When: 9:30am ET July 9, 2002
Where: Ballroom, National Press Club
529 - 14th Street, NW 13th floor
Washington, DC 20045
For More Information: Contact National Heart, Lung and Blood Institute at 301/496-4236.

EMBARGOED JAMA INFORMATION: 8:30 A.M. (CT) Tuesday, July 9, 2002
Media Advisory: To contact Jacques E. Rossouw, M.D., call the NHLBI Communications Office, 301/496-4236.
To contact Suzanne W. Fletcher, M.D., M.Sc., call Donna Burtanger at 617/432-3991.

Health Risks Outweigh Benefits for Combined Estrogen plus Progestin Clinical Trial Stopped Early in Major Study

CHICAGO -- Researchers have stopped the estrogen plus progestin portion of the Women's Health Initiative, a clinical trial designed to assess the major health benefits and risks of the most commonly used hormone preparation in the United States on healthy menopausal women, after overall health risks were found to exceed the health benefits, according to an article to be published in the July 17 issue of The Journal of the American Medical Association (JAMA). The study is being released early on the JAMA website (www.jama.com) because of the importance of the researchers' findings.

Figure 2: Headline following publication of the Million Women Study, Daily Express, 08 August 2003.

By **Julie Wheldon**
Health Editor

WOMEN taking HRT are doubling their risk of breast cancer, doctors warned last night.

The most common form of hormone replacement therapy has led to an extra 20,000 cases of the disease over the past 10 years, a new study shows.

Delyth Morgan, from the charity Breakthrough Breast Cancer, said: "This is a very disappointing day for all women.

"There has been a strong suspicion that HRT is implicated in breast cancer for many years and these results confirm our worst fears. We would urge any woman concerned to talk to her GP."

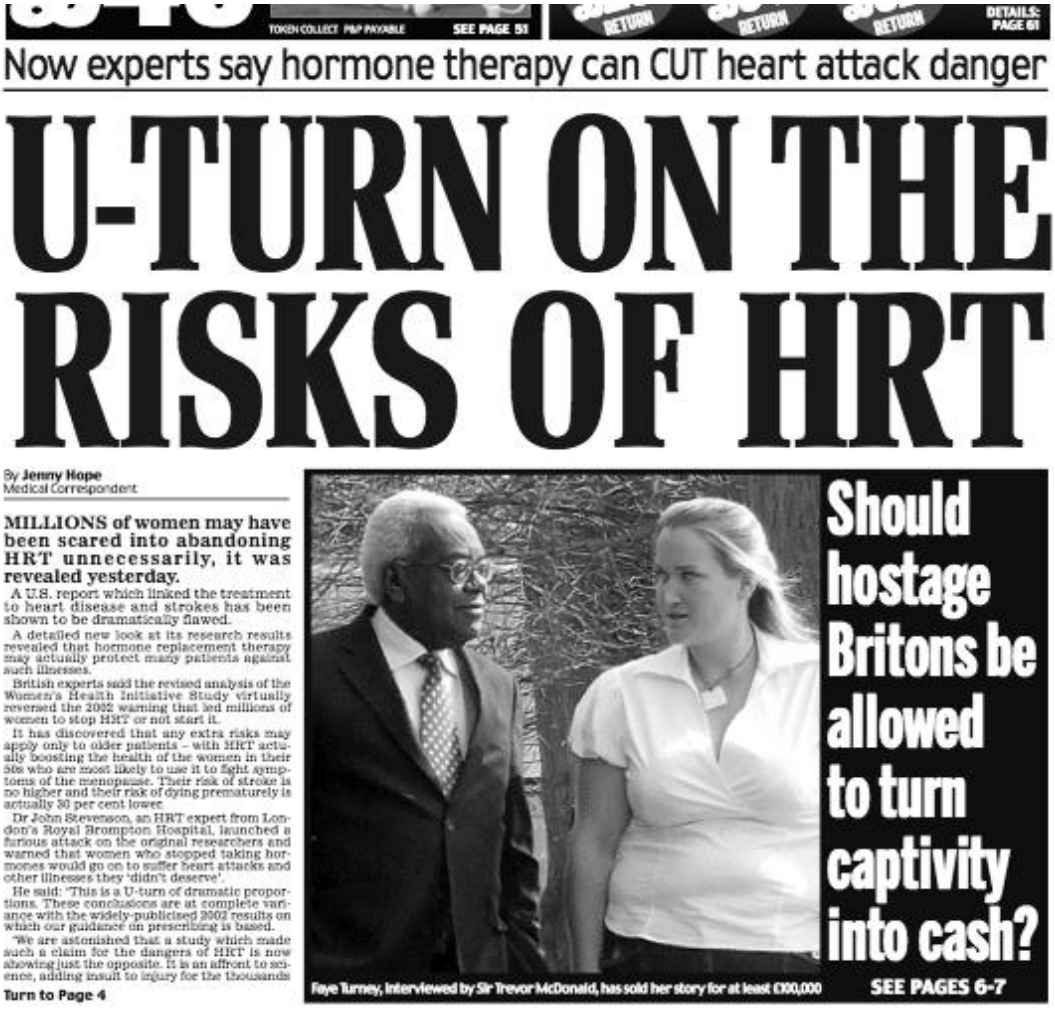
The alarming study, which involved a million women, has forced the Government's medicines watchdog to issue urgent new advice to the medical

TURN TO PAGE 11, COLUMN 1

MILLIONS HIT BY BREAST CANCER ALARM

SPECIAL EXPRESS REPORT PAGE 11

Figure 3: Not until the WHI's 2007 revised analysis of cardiovascular risk according to age was the menopause back on the front page. Daily Mail, 09 April 2007.



TOKEN COLLECT P&P PAYABLE SEE PAGE 51 RETURN RETURN RETURN DETAILS: PAGE 61

Now experts say hormone therapy can CUT heart attack danger

U-TURN ON THE RISKS OF HRT

By Jenny Hope
Medical Correspondent

MILLIONS of women may have been scared into abandoning HRT unnecessarily, it was revealed yesterday.

A U.S. report which linked the treatment to heart disease and strokes has been shown to be dramatically flawed.

A detailed new look at its research results revealed that hormone replacement therapy may actually protect many patients against such illnesses.

British experts said the revised analysis of the Women's Health Initiative Study virtually reversed the 2002 warning that led millions of women to stop HRT or not start it.

It has discovered that any extra risks may apply only to older patients – with HRT actually boosting the health of the women in their 50s who are most likely to use it to fight symptoms of the menopause. Their risk of stroke is no higher and their risk of dying prematurely is actually 30 per cent lower.

Dr John Stevenson, an HRT expert from London's Royal Brompton Hospital, launched a furious attack on the original researchers and warned that women who stopped taking hormones would go on to suffer heart attacks and other illnesses they 'didn't deserve'.

He said: 'This is a U-turn of dramatic proportions. These conclusions are at complete variance with the widely-publicised 2002 results on which our guidance on prescribing is based.

'We are astonished that a study which made such a claim for the dangers of HRT is now showing just the opposite. It is an affront to science, adding insult to injury for the thousands

Turn to Page 4

Should hostage Britons be allowed to turn captivity into cash?

Faye Turney, interviewed by Sir Trevor McDonald, has sold her story for at least £100,000

SEE PAGES 6-7

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28. Role of the Pharmaceutical Industry

The Pharmaceutical Industry (Pharma) plays a major role in the development, manufacture, sale, and distribution of pharmaceutical products. Pharma also plays a key role in biomedical research, biomedical research funding, and education related to biomedical products. In 2022 more than 8,000 medicines were in development around the world and PhRMA (Pharmaceutical Research and Manufacturers of America) members spent $102 Billion in 2021 alone on research and development [1]. The process of developing a new agent is complex, with long lead times and it has been claimed that the entire research and development as well as FDA approval process time - including compound synthesis, clinical development, and regulatory review - is 10 years or more, varying by therapeutic area [2].

Concerns have been raised in the past that industry sponsored trials may only publish outcomes when the results are favourable. However, at the 75th World Medical Association General Assembly in October 2024 there was a groundbreaking update to the Declaration of Helsinki [3], which stated that dissemination of results of trials is an ethical obligation and that negative and inconclusive results should be published and all affiliations disclosed. Most countries now have clinical trials registers with a requirement that all trial results, positive, negative or inconclusive, be published or available for review.

As the pharmaceutical industry is responsible for so many of the new drugs, they are inevitably the repository of the research data which lead to the regulatory approval of these products. As such, the pharmaceutical industry and the clinical investigators involved play a major role in the initial dissemination of the knowledge related to those products. Once they have regulatory approval, additional data becomes available from phase 4 studies and other, independently conducted ones. As a result, the education and experience related to those products starts to come from a broader range of more independent sources.

One of the principal concerns arising from the major role of Pharma has been the inevitable, potential conflict of interest, when data on new drugs are presented. In acknowledgment of this, major national and international medical congresses now mandate that Pharma sponsored sessions be clearly identified as such in the congress programs. Furthermore, all congress speakers are required to disclose any possible conflicts of interest prior to any presentation, particularly, where new products and devices are discussed. Similarly, all authors contributing to scientific journals, such as *Climacteric*, must declare any conflicts of interest relevant to the subject matter discussed.

The solution is not to ban Pharma involvement in medical education. It must be acknowledged that without Pharma's commitment to research and development we would not have enjoyed many of the advances in clinical care seen over the past 100 years. Additionally, the provision of unrestricted grants to support independently conducted educational activities is of great benefit to medical societies, their members and ultimately the patients they serve. However, it must also be acknowledged that Pharma generally represents big corporate companies whose principal aim is to maximize their profit. It is thus the responsibility of those providing medical education to ensure any involvement with Pharma is transparent and balanced. Ultimately, there is a need for us all to work together to improve

healthcare outcomes, acknowledging the different roles we all play in achieving this goal whilst at the same time disclosing any real or perceived conflicts of interest.

Recommendations and Key Messages

- The need for new pharmaceutical agents for the management of menopause is critical. KM
- The pharmaceutical industry is responsible for the development, manufacturing and distribution of those agents. KM
- The pharmaceutical industry invests a significant amount in biomedical research conducted by industry, academic researchers and others. KM
- The pharmaceutical industry plays a significant role in the education related to those agents. KM
- Any involvement with the pharmaceutical industry in any educational activity should be transparent and declared by all those involved. KM

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29. Publication Ethics

Publication ethics is of importance to editors, publishers, authors, academic institutions, and medical societies among others. Three organizations which contribute significantly to this discussion are the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME) and Committee on Publication Ethics (COPE).

A variety of topics are related to publication ethics, including authorship, disclosure, research integrity, duplicate publication, plagiarism, predatory journals, and most recently artificial intelligence.

Artificial Intelligence (AI)

The ICJE recommends the following regarding the use of AI in submissions:

1) Authors should disclose if AI was utilized in a submitted work.
2) Authors using AI should describe in the cover letter and the submission how AI was utilized.
3) Chatbots can't be authors as they can't be responsible for the accuracy, integrity and originality of the work.
4) Humans must be responsible for the submitted material that include AI assistance [1].

Predatory Journals

Elmore and Weston stated "The main goal of predatory journals is profit. They attempt to deceive authors to publish for a fee without providing robust peer review or editorial services, thereby putting profit over trustworthy and dependable science." [2]. Sometimes these are Open Access journals.

Authorship

According to the ICMJE recommendations the authorship should be based on the following 4 criteria:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
2) Drafting the work or reviewing it critically for important intellectual content;
3) Final approval of the version to be published;
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. [1]

Disclosure

Disclosure of potential and actual conflicts of interest is key to maintaining trust in published articles. This applies to authors, editors and reviewers among others. Conflicts of interest may exist when one interest is in conflict with another. That may occur when a personal interest (such as financial, speaking opportunities or academic promotion) is in conflict with a professional obligation, it may also occur when the scientific interest of an organization (for example a journal, a company or a government funding organization) is in conflict with another interest (such as financial, acceptance of ideas, meeting goals, etc.) [3]. Transparency and disclosure are fundamental for maintaining ethics in publishing.

Research Integrity

In addition to honesty in the manner in which research is conducted, researchers should ensure that studies involving human subject are well planned and conducted in accordance with the Declaration of Helsinki and approved by appropriate ethics committees or institutional review boards. Patients' right to privacy must be respected and appropriate informed consent obtained. Clinical trials should be registered in an appropriate/pertinent public database at or before enrolling patients. "The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome." Animal studies must conform to appropriate standards for the care and use of laboratory animals. Relevant items (above) should be reported in the manuscript [1].

Duplicate Publication

Generally, manuscripts should not be submitted to more than one journal at a time, even if they are in different languages, however joint publication of select articles such as consensus statements may be acceptable, if approved by the respective editors. Previously published papers should not be submitted without the expressed approval of the editor(s). Presentations at meetings do not generally jeopardize future publication of the data nor does the limited posting of trial results in a clinical trial registry. However, internet posting of a manuscript or study results may prevent future journal publication. Copyright considerations should also be considered [4].

Plagiarism

COPE has stated the following: "Plagiarism ranges from the unreferenced use of others' published and unpublished ideas, including research grant applications to submissions under 'new' authorship of a complete paper, sometimes in a different language" [5]. Plagiarism detection software is increasingly being used by editorial staff and it may also detect self-plagiarism. It is an author's responsibility to ensure that plagiarism is avoided, that appropriate referencing is utilized, and when appropriate, permission to utilize material is obtained.

Recommendations and Key Messages

- Publication ethics are of concern to everyone involved in the preparation, publication, and reading of the scientific literature. KM
- The use of AI in scientific research and manuscript preparation is a developing area. However, its use must be disclosed in manuscripts and manuscript cover letters, and human authors must take responsibility for the accuracy of the information imparted. KM
- Care must be taken to avoid plagiarism and generally also duplicate publication. KM
- Research integrity is critical to the scientific process. Disclosure and transparency are an important part of research integrity. KM

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Influence of Methodology and Epidemiology on MHT Perception

There is a well-recognized hierarchy of scientific evidence to consider when drawing conclusions from any scientific investigation. Typically, the levels of evidence are replicated results from high-quality randomized controlled trials (RCTs), followed by prospective cohort studies. Even evidence from RCTs and cohort studies should be interpreted with caution, particularly with reference to MHT (see Methodology Table 1), although when properly conducted and analyzed these two designs have the lowest potential for bias. Further down the hierarchy, in order of potential validity are other observational designs, including case-control studies, cross-sectional studies, case series and case reports. Systematic reviews and meta-analyses have recently become popular; however, as they often combine studies of varying design, quality and analytic methods, each must be assessed on its individual merits.

The epidemiological literature regarding MHT is dominated by the Women's Health Initiative (WHI) Clinical Trials since they were RCTs and because they followed a very large number of subjects. The release, with great fanfare, of the findings of the WHI trial of conjugated equine estrogens and medroxyprogesterone acetate (CEE + MPA), following the early stopping of the trial in 2002 reversed, almost overnight, the prior strong perception of MHT benefit, particularly for prevention of coronary heart disease (CHD), the dominant cause of death in postmenopausal women. The prior perception had been built on a substantial foundation of prospective cohort studies and one small clinical trial – nearly all of which had evaluated MHT use in women who initiated treatment near the time of menopause. In contrast, the WHI was designed to test the effect of MHT in women who were, on average, a decade or more post-menopausal, with the prevention of CHD as the primary outcome. Secondary outcomes were breast cancer, fracture and colorectal cancer. Breast cancer was a safety measure, while prevention of fracture and colorectal cancer were secondary objectives for benefit. The CEE + MPA trial was stopped after approximately 5 years of average follow-up on the recommendation of the Data Safety and Monitoring Committee when breast cancer rates exceeded a pre-specified monitoring boundary, although the finding was not statistically significant. The stopping recommendation was also supported by results that suggested the benefit for CHD, the primary outcome (which was expected to be evaluable after approximately 9 years), would not be found even if the trial were to continue [1].

The decision to prematurely stop the trial was taken in late spring 2002 and the hastily prepared paper announcing those results, drafted without engagement of the clinical center investigators, was published in July 2002. This was a time before electronic publication was a routine, and the results were released at a press conference about a week before the paper would be available to journal subscribers. At the press conference and in the press release, the breast cancer findings were emphasized without qualification, even though they were non-significant with per-protocol adjustment for this secondary outcome [2,3].

The fact that monitoring boundaries in clinical trials are established with an abundance of caution, and that those boundaries rarely meet the test for scientifically valid differences, was lost in the firestorm that tapped into women's strong fear of breast cancer. Science and valid statistical inference never had a chance. When protocol is violated and findings are misrepresented, even the results of a clinical trial can be misleading. The breast cancer findings reported from the CEE + MPA trial are a prime example of that. The emphasis on the putative breast cancer harm and the small increase in CHD at this

premature stopping time led the US Food and Drug Administration (FDA) to add its highest level of warning, a “black box” warning citing breast cancer and cardiovascular risks to the labelling of all estrogen-containing medications.

Women’s fear of breast cancer, the FDA “black box” warning, and the misleading publicity surrounding the WHI announcement in 2002, triggered a profound decline in use of MHT that persists to this day. This is even more remarkable considering that the breast cancer findings in the WHI CEE-alone trial, reported in 2004, were for a reduction in breast cancer that was statistically significant among adherent participants and in long-term follow-up [4,5]. Similarly, the WHI CEE-alone trial found a significantly reduced rate of CHD in women aged 50 to 59 [6].

RCTs, e.g. the WHI, are conducted to test treatment effects by evaluating hypothesized cause-and-effect relationships in an experimental design that minimizes confounding by factors that could independently affect the outcome. Accordingly, a properly designed, conducted and reported RCT provides the highest level of scientific evidence. The level of evidence of a RCT can be downgraded due to factors such as deviation from protocol, poor compliance, loss to follow up exceeding the study design expectations, lack or failure of blinding, and errors in statistical analysis. Errors in reporting, including misrepresentation of results, inappropriate generalization of a single treatment to an entire class of treatments, and inappropriate generalization of results to populations for which the trial was not adequately powered, can downgrade the utility of a trial’s reports, without affecting the value and utility of the trial’s data. For example, the WHI was designed to test the outcomes associated with the use of MHT in women more than a decade past menopause. However, its results were inappropriately 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 compounds, other doses, and other routes of administration strays beyond the bounds of proper methodology, particularly when evidence from other study designs, spanning from histological, to metabolic and to cohort, suggests meaningful differences by compound, dose and route of administration. Recognizing these concerns and the weight of the literature overall, the US FDA removed the “black box” warning from estrogen products in November of 2025 in favor of more nuanced labeling that is tailored to the form and indications of each product, with qualification based on patient subgroups, and that acknowledges the importance of timing of initiation in relation to menopausal status [7].

Observational studies, e.g., the Nurses’ Health Study, are mainly used for generating hypotheses, and cannot establish true causality.

Observational studies of MHT often have inherent biases, including:

- selection bias - where healthier women are more likely to be prescribed MHT;
- recall bias - where recall of prior hormone usage may be influenced by later outcomes;
- reporting bias - where women on MHT may be more likely to report outcomes believed to be associated with hormones, with women not on MHT less likely to do so;
- prevention bias - where women on MHT are monitored and treated more intensively;
- compliance bias - where patients with higher adherence, even to a placebo, show better outcomes;

- survivor bias - where MHT may be discontinued due to illness;
- prevalence-incidence bias - where early adverse effects of MHT may go unobserved if the user dies before becoming part of a cohort.

Attention should be given to whether advanced and/or appropriate statistical techniques are employed that allow for the adjustment of confounding variables, and for excluding chance, as well as mediating or instrumental variables, ensuring that the reported effects are due to MHT rather than other factors. Nonetheless, not just the Nurses' Health Study, but also multiple large prospective cohort studies conducted in other populations and with different designs found similar benefits for CHD protection. This was associated with use of MHT initiated near the time of menopause and continued for several years thereafter.

The WHO 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. However, these frequencies do not necessarily correspond to statistical significance. Rare findings in large RCTs and observational studies may be statistically significant due to the large sample size, but they may be of minor clinical importance when applied to individual patients in a clinical setting. The adverse effects observed for MHT generally fall in the uncommon to rare categories. Failure to provide a clinical context is often a problem in understanding and interpreting study outcomes.

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Discussion

In this United Nations Decade of Healthy Aging, it is estimated that more than a billion women will soon be in a menopausal age group globally. There is currently a concerning "women's health gap"; women live 25% more of their lives in poor health when compared to men [1]. This is partly due to the increasing incidence of non-communicable diseases such as osteoporosis, cardiovascular disease and dementia, which become increasingly prevalent after menopause. The increasing prevalence of POI, where greater risk of chronic disease is associated with younger age of menopause, is of additional concern.

Menopause associated problems potentially reduce both the life and health spans of women. It has been estimated by the World Economic Forum & McKinsey Institute that dealing with menopause-associated problems in the women's health gap can result in approximate gains of 2.4 million annual Disability Adjusted Life Years (DALYs) and $120 billion in annual gross domestic product globally [1] (Link 1). With a rapidly growing population of women at midlife, menopause and beyond, it is imperative that research and evidence-based management supported by guidelines continues to optimize women's quality of life and long-term well-being.

The mission of the IMS is to work globally to promote and support access to best practice healthcare for women through their menopause transition and post-reproductive years, enabling them to achieve this with optimal health and well-being. Through effective communication and evidence-based education about menopause, women can be empowered to make informed personalized choices aligned with their individual goals.

This paper provides the full guideline text, recommendations and key messages for the support and advice to women on midlife health and menopause and is made available as an easily updatable "living" document on the IMS website. The summary recommendations version and a few of the sections have also been submitted to *Climacteric* and other journals as individual papers containing additional data and meta-analyses generated by the systematic review process. The recommendations are based on the best available evidence or, where data of sufficient quality are absent, on good practice points from our expert authors.

The current IMS recommendations represent an update of the 2016 IMS recommendations; the key questions and topics covered in the 2016 version were updated based on the results of a scoping survey of HCPs via their stakeholder organizations and the public. The evidence supporting the recommendations was modified based on data published between 2016 and 2025, and prior to 2016 where required by the PICO questions and new topics. Important new topics added included sections on sarcopenia, perimenopausal contraception and the novel neurokinin targeted therapies.

These new IMS evidence-based recommendations are intended to form the blueprint to support the optimal care of all women in midlife and menopause globally and followed on from the recent IMS editorial [2] and 2024 and 2025 White Papers for the respective World Menopause Days [3,4]. The theme of the editorial and subsequent papers called for a well-balanced narrative on the menopause momentum and addressed key controversies on menopause, lifestyle, MHT and alternatives.

The last few years have seen a renaissance in interest in menopause in many countries. Although this is generally good as it has led to the dissemination of a considerable amount of information, some of this was misinformation and disinformation, often for the purpose of commercial gain.

The aim of these recommendations was therefore to rigorously interrogate the existing data through a formal systematic review process and to commission experts in their field to interpret these data and produce the best evidence possible for the effective and safe management of the menopause. However, it should be emphasized that adherence to guidance does not guarantee a successful or specific outcome, nor does it establish a standard of care. Also, practice guidelines do not replace the need for application of clinical judgment to each individual clinical presentation, nor variations based on locality, facility type, resources and cultural considerations.

It is also 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 in other parts of the world. 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 the use of MHT.

It is important that the adaptation of these recommendations is made relevant to each individual country and region, hence the involvement from the outset of numerous national and regional societies, and the public in the development of the key questions and subsequent endorsement of the guidance. There is, of course, a key role for other position statements and guidance that represent clinically important local, regional and international practice [5-11].

Nonetheless, it is hoped that the publication of these recommendations will be followed by an update of the consensus statement in which areas of common interest and relevance worldwide can be further explored and agreed upon [12]. Equally important is continuing to investigate what we do not know, and projects such as the global Menopause Priority Setting Partnership (MAPS) [13] and the Exploration of the Mental and Physical Health impact in Menopausal women (MARIE) [14] collaborative are also important if we are to achieve a greater understanding of the impact of diverse social and cultural influences on health outcomes in menopause, midlife and beyond.

The development, dissemination and implementation of globally relevant recommendations and guidelines therefore mandates collaboration with organisations that have common interests and goals. The recent update of the ESHRE POI guideline [15] (Link 2) was achieved through a partnership of ESHRE with the American Society for Reproductive Medicine (ASRM), Monash University and the IMS and the involvement of numerous stakeholder organizations. Similarly, it is hoped that through collaboration with our stakeholder organisations and 65 IMS-affiliated menopause societies (Link 3), the updated IMS recommendations will be adopted as widely as possible. The IMS peer-reviewed journal *Climacteric* will act as a conduit for the information, and development and translation of HCP educational tools such as IMS Professional Activity for Refresher Training (IMPART) (Link 4) and updated clinical toolkits [16] will facilitate this. Information for the public (e.g. infographics, algorithms, videos, etc.) will be equally important in global implementation; this information will be made available through the IMS consumer portal, Menopause Info (Link 5)

Conclusions

A well-balanced conversation informed by evidence-based recommendations is crucial to the ethical management of women's midlife health and menopause.

Any treatment, hormonal or otherwise, should be underpinned by optimizing lifestyle, diet, exercise, avoiding smoking and minimizing alcohol consumption.

The principles and practice of lifestyle management of menopause were well covered in the 2025 IMS White Paper [4].

The efficacy and safety of MHT and alternative therapies depend on various factors; before prescribing, consideration should be given to the following principles as per the five Ws in the 2024 White Paper and executive summary, which addressed the key controversies [3].

- Who is MHT for?
- What types and doses of MHT?
- When should it be started and stopped?
- Why is MHT important?
- Where can MHT be accessed?

It is hoped that these new IMS Recommendations and Key Messages on women's midlife health and menopause will provide readers with greater clarity regarding the safe and effective management of the menopause, as well as a pathway to further research opportunities. Key action points (outlined below) are essential to ensure continued progress for the health of individual women, their families, and society as a whole.

Key Action Points

- Women: improve access to evidence-based, balanced information to increase health literacy, empower informed decisions and self-management, thereby increasing proactive confidence to maintain menopausal health.
- Government / institutions: encourage evolution of policy towards supporting research and clinical management of women's health, in particular during the menopause transition and beyond.
- HCPs: continue to strive to increase education and training for health-care professionals to optimize evidence-based menopause management.
- Media: engage positively, highlighting the importance of evidence-based, non-sensationalist information.
- Pharma industry: encourage research and development of therapeutic interventions that minimize adverse effects and maximize benefits and improve the supply of affordable medications globally, especially to low- and middle-income countries.
- MHT and alternatives: clarification of differences in action/risk profiles to maximize benefits and minimize adverse effects and provision of the widest possible armamentarium of treatment options to facilitate personalized care.

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Summary of Full Recommendations and Key Messages paper

The summary document is available at:
https://www.tandfonline.com/doi/full/10.1080/13697137.2025.2585487

Disclosure Statement

Haitham Hamoda: No conflicts of interest to declare.

Tim Hillard is a current IMS Board member and Editor-in-Chief of *Climacteric*. He has received honoraria for lecturing and participating in advisory boards from Astellas and Besins.

Rakibul Islam: No conflicts of interest to declare.

Nick Panay is immediate past president of IMS and a current IMS Board Member. He has lectured and acted in an advisory capacity for Abbott, Astellas, Bayer, Besins, Gedeon Richter, Mithra, Novo Nordisk, SeCur, Theramex and Viatris.

Amanda Vincent is a current IMS board member and has received honoraria, or participated in advisory boards for: Astellas, Besins, IQ Fertility and Theramex.

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ORCID

Anna Fenton http://orcid.org/0000-0002-6732-8284

Haitham Hamoda https://orcid.org/0000-0002-2330-1768

Tim Hillard https://orcid.org/0000-0002-2097-609X

Rakibul Islam https://orcid.org/0000-0002-0889-8658

Nick Panay http://orcid.org/0000-0001-6662-1334

Lorena Romero https://orcid.org/0000-0001-9884-5463

Amanda Vincent https://orcid.org/0000-0002-3760-7266

Key Links

Link 1: https://www.mckinsey.com/mhi/our-insights/closing-the-womens-health-gap-a-1-trillion-dollar-opportunity-to-improve-lives-and-economies

Link 2: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Premature-ovarian-insufficiency

Link 3: https://www.imsociety.org/membership/cams/

Link 4: https://www.imsociety.org/education/impart-registration/

Link 5: https://www.menopauseinfo.org/

Endorsing Stakeholder Societies

The following organizations provided their endorsement of the *IMS Recommendations and Key Messages on Women's Midlife Health and Menopause* summary document: (https://www.tandfonline.com/doi/full/10.1080/13697137.2025.2585487)

Asia Pacific Menopause Federation (APMF)

Australasian Menopause Society (AMS)

British Menopause Society (BMS)

Canadian Menopause Society (CMS)

European Menopause and Andropause Society (EMAS)

Federacion Latino Americana de Asociaciones y Sociedades de Climaterio y Menopausia (FLASCYM)

International Menopause Society (IMS) Executive and Board

International Society for Gynecological Endocrinology (ISGE)

Royal College of Obstetricians and Gynaecologists (RCOG)

South African Menopause Society (SAMS)

Thai Menopause Society

The summary document was also endorsed by key public women's health stakeholder representatives.

Abbreviations

AACE	American Association of Clinical Endocrinologists
ACECP	American College of Endocrinology
ACT	Acceptance and Commitment Therapy
AD	Alzheimer's Disease
AFC	Antral Follicle Count
AFF	Atypical Femoral Fracture
AGREE II	Appraisal of Guidelines for Research & Evaluation II
AI	Artificial Intelligence
AI	Aromatase Inhibitors
AMH	Anti-Mullerian Hormone
AMY	The Australian Women's Midlife Years (AMY) study
APMF	Asia-Pacific Menopause Federation
ARCH	**A**ctive-cont**R**olled Fra**C**ture Study in Postmenopausal Women with Osteoporosis at **H**igh Risk of Fracture
ART	Assisted Reproduction Technology
ASRM	American Society for Reproductive Medicine
AWGS	Asian Working Group for Sarcopenia
BHT	Bioidentical Hormone Therapy
BMD	Bone Mineral Density
BMI	Body Mass Index
BMS	British Menopause Society
BP	Bisphosphonates
BRCA	BReast CAncer gene
CAM	Complementary and Alternative Medicine
cBHT	Compounded Bioidentical Hormone Therapy
CBT	Cognitive Behavioral Therapy
CBT-I	Cognitive Behavioral Therapy for Insomnia
CDC	Centers for Disease Control and Prevention
CEE	Conjugated Equine Estrogen
CGG	Cytosine Guanine Guanine
CGI	Clinical Global Impression
CHC	Combined Hormonal Contraception
CHD	Coronary Heart Disease
CHM	Chinese Herbal Medicine
CIOMS	Council for International Organizations of Medical Sciences
CI	Confidence Intervals
CIT	L-Citrulline supplementation
COC	Combined Oral Contraceptive
COPE	Committee on Publication Ethics
CRC	Colorectal Cancer
Cu-IUD	Copper Intrauterine Device
CVA	Cardiovascular Accident
CVD	Cardiovascular Disease
DALYs	Disability Adjusted Life Years
DASH	Dietary Approaches to Stop Hypertension
DHEA	Dehydroepiandrosterone

DHEAS	Dehydroepiandrosterone Sulfate
DMPA	Depot Medroxyprogesterone Acetate
DRI	Dietary Reference Intake
DUB	Dysfunctional Uterine Bleeding
DVT	Deep Vein Thrombosis
DXA	Dual Energy X Ray Absorptiometry
ECG	Electrocardiogram
E2	Estradiol
EE	Ethinyl Estradiol
ELITE	The Early versus Late Intervention Trial with Estradiol
EM	Early Menopause
EMA	European Medicines Agency
EMAS	European Menopause and Andropause Society
EPIC	European Prospective Investigation into Cancer and Nutrition (EPIC) Study
EPT	Estrogen Progestogen Therapy
ER	Estrogen Receptor
ERα	Estrogen receptor α
ERβ	Estrogen receptor β
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
ESHRE	European Society of Human Reproduction and Embryology
ET	Endometrial Thickness
ET	Estrogen Therapy
EWGSOP2	European Working Group on Sarcopenia in Older People
FDA	Food and Drug Administration
FLASCYM	Federación Latinoamericana de Sociedades de Climaterio y Menopausia
FMD	Flow-Mediated Dilation
FMP	Final Menstrual Period
FNIH	Foundation for the National Institutes of Health
FRAX	Fracture Risk Assessment Tool
FSH	Follicle-stimulating hormone
FSRH	Faculty of Sexual and Reproductive Healthcare
GDP	Gross Domestic Product
GI	Gastrointestinal
GLP	Glucagon-Like Peptide
GnRH(a)	Gonadotropin Releasing Hormone (Analogue)
GPP	Good Practice Point
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
GSM	Genitourinary Syndrome of Menopause
GWAS	Genome-Wide Association Study
HA	Hyaluronic Acid
HCC	Hepatocellular Carcinoma
HCP	Healthcare Professional
HDL	High-Density Lipoprotein
HER2+	Human Epidermal Growth Factor Positive
HMB	Heavy Menstrual Bleeding
HPV	Human Papillomavirus
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
HRV	Heart Rate Variability

HSDD	Hypoactive Sexual Desire Disorder
HT	Hormone Therapy
ICMJE	International Committee of Medical Journal Editors
IDL	Intermediate Density Lipoprotein
IGF-1	Insulin-like Growth Factor 1
IL-1	Interleukin 1
IL-6	Interleukin 6
IMPART	IMS Professional Activity for Refresher Training
IMS	International Menopause Society
IOF	International Osteoporosis Foundation
ISGE	International Society of Gynecological Endocrinology
IU	International Unit
IV	Intravenous
IWGS	International Working Group on Sarcopenia
KEEPS	Kronos Early Estrogen Prevention Study
KNDy	Kisspeptin, Neurokinin B, and Dynorphin Neurons
LARC	Long-Acting Reversible Contraception
LCMS	Liquid Chromatography and Tandem Mass Spectrometry
LDL	Low-Density Lipoprotein
LNG IUD	Levonorgestrel Intrauterine Device
MAPS	Menopause Priority Setting Partnership
MARIE project	An exploration of the Mental and Physical Health impact in Menopausal women
MBC	Midlife Body Changes
MBI	Mindfulness-based interventions
MBSR	Mindfulness-Based Stress Reduction
MBT	Markers of Bone Turnover
MedDiet	The Mediterranean Diet
MENQOL	Menopause-specific Quality of Life (questionnaire)
MeSH	Medical Subject Headings
mg	Milligrams
MHT	Menopause Hormone Therapy
MI	Myocardial Infarction
ML	Machine Learning
MMR	Measles, Mumps, and Rubella (vaccine)
MOF	Major Osteoporotic Fractures
MPA	Medroxyprogesterone Acetate
MRS	Menopause Rating Scale
MT	Menopause Transition
NCD	Noncommunicable Diseases
NET	Norethisterone
NETA	Section 15
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NK1	Neurokinin 1
NK3	Neurokinin 3
NLP	Natural Language Processing
NOGG	National Osteoporosis Guidelines Group
NOMAC	Nomegestrol Acetate
NSCLC	Non-Small Cell Lung Cancer
OAB	Overactive Bladder

OAC	Oesophageal Adenocarcinoma
Off-Label	Approved medication for purpose, dosage, age, or route not specified in official license
ONJ	Osteonecrosis of the Jaw
OR	Odds Ratio
ORAI	Osteoporosis Risk Assessment Instrument
OST	Osteoporosis Self-Assessment Tool
PARP	Poly (ADP-ribose) polymerase
PCOS	Polycystic Ovary Syndrome
PD	Parkinson's Disease
PE	Pulmonary Embolism
PDGF	Platelet Derived Growth Factor
PFMT	Pelvic Floor Muscle Training
Pharma	Pharmaceutical
PhRMA	Pharmaceutical Research and Manufacturers of America
PICO	Population, Intervention, Comparison, and Outcome
PMB	Postmenopausal Bleeding
PMDD	Premenstrual Dysphoric Disorder
POI	Premature Ovarian Insufficiency
POP	Progestogen Only Pills
PR	Progesteron Receptor
PRP	Platelet-Rich Plasma
PSC	Publication Steering Committee (IMS)
PTH	Parathyroid Hormone
PTHrP	Parathyroid Hormone-related Peptide
PUFAs	Polyunsaturated Fatty Acids
QOL	Quality Of Life
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of Nuclear factor Kappa B Ligand
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized Controlled Trials
RDI	Recommended daily intake
RNA	Ribonucleic Acid
RR	Risk Ratio
rUTI	Recurrent Urinary Tract Infection
SAMS	South African Menopause Society
SARC-F	Strength, Assistance with walking, Rise from a chair, climb stairs, and Falls
SCC	Squamous Cell Carcinoma
SDOC	Sarcopenia Definitions and Outcomes Consortium
SERM	Selective Estrogen Receptor Modulator
SHBG	Sex-Hormone Binding Globulin
SLD	Steatotic Liver Disease
SLE	Systemic Lupus Erythematosus
SMI	Skeletal Muscle Mass Index
SNRI	Serotonin–Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitors
STEAR	Selective Tissue Estrogenic Activity Regulator
STI	Sexually Transmitted Infections
STRAW	Stages of Reproductive Aging Workshop
SWAN	Study of Women's health Across the Nation
TAS	Transabdominal

TBS	Trabecular Bone Score
TGF	Transforming Growth Factor i.e., TGF-β1
TMS	The Menopause Society (formerly The North American Menopause Society – NAMS)
TNF	Tumour Necrosis Factor i.e., TNF-α
TSEC	Tissue Selective Estrogen Complex
TVS	Transvaginal Ultrasound
UI	Urinary Incontinence
UN	United Nations
UQOL	Utian Quality of Life Scale
USPSTF	The US Preventive Service Task Force
UTI	Urinary Tract Infection
VERO	**VER**tebral fracture treatment comparison in **O**steoporotic women
VFA	Vertebral Fracture Assessment
VLDL	Very Low-Density Liporprotein
VMS	Vasomotor Symptoms
VTE	Venous Thromboembolism
VVA	Vulvovaginal Atrophy
WAME	World Association of Medical Editors
WHI	Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study
WHO	World Health Organization