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Obstetrical and Gynaecological Society of Malaysia (OGSM)

PERSATUAN MENOPOS MALAYSIA

College of Obstetrician & Gynaecologists

CLINICAL PRACTICE GUIDELINES

Management Of MENOPAUSE in Malaysia

2022

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STATEMENT OF INTENT

This clinical practice guideline (CPG) is a guide to clinical management of menopause and its related problems in the local setting. It is based on the best available evidence present at the time of development and print. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his / her patient based on the clinical picture presented and the patient's unique characteristics, using management options available locally.

UPDATING THE CPG

These guidelines are issued in 2022 and will be reviewed within a minimum period of 4 years (2026) or sooner if new evidence arises which may affect management. In due course, at time of reviewing the CPG, the Chairperson or the Head of the Menopause Subdivision of the Obstetrical and Gynaecological Society will work together with the Malaysian Menopause Society to carry out the necessary revision in accordance with the latest systematic review methodology used by MaHTAS.

Every care has been taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version which would be the definite version at all times.

This CPG will be made available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
https://www.ogsm.org.my
https://www.menopausefacts.org.my
http://menopause.org.my/wordpress

This CPG will also be made available as an app for Android and IOS platform: MyMAHTAS

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FOREWARD

Menopause, a natural biological process that is accompanied by estrogen deficiency, will affect every woman. As the average age of menopause in Malaysia is around 50 years, one-third of the lives of women are going to be without the hormone estrogen, making them susceptible to a multitude of problems; ranging from social to medical issues such as coronary heart disease, non-communicable diseases, osteoporosis, and cancers.

This Clinical Practice Guideline (CPG) on Management of Menopause in Malaysia, a collaboration between the Obstetrical and Gynaecological Society of Malaysia, the Malaysian Menopause Society along with the College of Obstetrics and Gynaecology, Academy of Medicine, Malaysia is an excellent start on what we can do for our aging women. Awareness of problems that menopause can bring, preventive strategies, early detection, and menopause management are essential. We need to take away the menopause "vacuums' that have been created over the years and talk more openly about menopausal health.

Menopausal hormone therapy remains an effective option for menopausal symptoms. Robust clinical data has indicated the effectiveness and safety of these therapies in early menopause. It is therefore important to reappraise the current evidence available and the production of this guideline is timely to encourage healthcare professionals to play an important role in promoting, counseling, and providing health education regarding menopausal hormonal therapy.

Thank you to the members of the expert panel, the review committee, HTA at MOH, and the external reviewers for producing this clear and concise guideline. It is my fervent hope that this CPG will help educate our healthcare workers to be proactive in managing menopausal health, as preventive and early detection strategies can be implemented as a woman goes through menopause

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MINISTER OF HEALTH MALAYSIA

Levels of Evidence

Definitions of levels of evidence by the Canadian Task Force on Preventive Health Care 2001

Levels	Study Design
I	Evidence obtained from meta-analysis of randomised controlled trials (RCTs).
II – 1	Evidence from controlled trial (s) without randomisation.
II – 2	Evidence from cohort or case control analytic studies, preferably from more than one centre or research group.
II – 3	Evidence from comparisons between times and places with or without the intervention: dramatic results from uncontrolled studies could be included here.
III	Opinions of respected authorities, based on clinical experience: descriptive studies or reports of expert committees.

FORMULATION OF RECOMMENDATION

In line with the new development in CPG methodology, the CPG unit of MaHTAS is adapting **GRADING RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT and EVALUATION (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed / reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

All statements and recommendations formulated after that were agreed upon by both the CPG Development Group and the Review Committee. This CPG was developed largely based on the findings of systemic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Developmental Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

The Perimenopause

1.	Women experiencing abnormal uterine bleeding in the perimenopause should always be investigated based on the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified).[15 (Level III)]
2.	Clinical investigations for a woman with abnormal uterine bleeding include a vaginal examination, pap smear (in sexually active women) and a pelvic ultrasound to rule out local pelvic pathology. If a vaginal examination cannot be carried out, a pelvic ultrasound on a full bladder would suffice. Blood investigations for anemia, thyroid dysfunction and coagulation disorders (if necessary) are advised.[15 (Level III)]
3.	Women with perimenopausal symptoms are advised either the • low dose oral contraceptive pill as it acts as a contraceptive, gives better cycle control and treats perimenopausal symptoms.[14 (Level I)] • menopausal hormone therapy which gives better cycle control and treats perimenopausal symptoms but is inadequate as a contraceptive. Non-hormonal contraception is advised, if necessary.[15 (Level I)]
4.	The levonorgestrel intrauterine system (LNG-IUS) is an alternative treatment for perimenopausal women with heavy menstrual bleeding. It acts as a contraceptive and provides endometrial protection. Women requiring menopausal hormone therapy can continue using the LNG-IUS and add estrogen either orally or via the transdermal route.[16 (Level I)]

Premature Ovarian Insufficiency (POI)

1.	Women with premature ovarian insufficiency are at risk of long-term consequences of estrogen deficiency, especially osteoporosis (8%), premature coronary artery disease, cardiovascular disease and dementia.[18 (Level I), 20 (Level 1)]
2.	The low dose combined oral contraceptive pill (COC) is recommended for women with premature ovarian insufficiency till the age of menopause (50 years). It acts both as a hormone replacement and a contraceptive.[20 (Level1)]
3.	Menopausal hormone therapy (MHT) may be used as an alternative to the combined oral contraceptive (COC) pill in women with premature ovarian insufficiency. Additional measures should be advised if contraception is required.[20 (Level1)]

Menopausal Hormone Therapy (MHT)

1.	Women with menopausal symptoms who are less than 60 years of age or within 10 years of menopause should be offered menopausal hormone therapy for relief of vasomotor symptoms, genitourinary symptoms of the menopause and prevention of bone loss. The risk of cardiovascular disease, stroke and venous thromboembolism is lower in this age group when compared to older post-menopausal women.[20, 97, 98, 175, 177 (Level I), 179 (Level II-2)]
2.	For maximal cardio protective efficacy, women should start menopausal hormone therapy with the onset of vasomotor symptoms and within 10 years of menopause.[122 (Level I)]
3.	Women with menopausal symptoms who are at a higher risk of stroke or venous thromboembolism are advised to use transdermal estrogen preparations (non-oral) for relief of menopausal symptoms. Women with an intact uterus will still need to add 12 -14 days of either oral or vaginal progestogen or use the levonorgestrel intrauterine system (LNG-IUS) for endometrial protection.[114 (Level II-3), 118 (Level II-1)]

4.	In women with coexisting morbidities such as obesity, hypertriglyceridemia, active gall bladder disease, known thrombophilia such as Factor V Leiden and have a higher risk of venous thromboembolism; transdermal estrogen is preferred over oral estrogen preparations as it is as effective for vasomotor symptoms with a lower risk of venous thromboembolism.[114 (Level II-3), 118 (Level II-1)]
5.	The low dose vaginal estrogen therapy is advised for relief of symptoms of genitourinary syndrome of menopause; additional progestogen therapy is not required for endometrial protection. However, any unscheduled vaginal bleeding should always be investigated.[116 (Level I)]
6.	Younger women who undergo surgical menopause are advised to take estrogen only therapy till the age of 50 years to prevent immediate and long-term problems of the menopause.[124 (Level I)]

Types of Menopausal Hormone Therapy (MHT)

1.	Hysterectomised women (women without a uterus), need only estrogen therapy for relief of menopausal symptoms. [101 (Level I)]
2.	Non-hysterectomised women (women with an intact uterus) need both estrogen and progestogen therapy for relief of menopausal symptoms. Progestogens are added only for endometrial protection.[101 (Level I)] • Cyclical therapy (regular scheduled periods) is prescribed for women in the perimenopause.[112 (Level I)] • Continuous combined therapy (no bleed therapy) is prescribed for women who are one year from their last period.[112 (Level I)]

Effects of Menopausal Hormone Therapy

1.	Menopausal hormone therapy treatment is recommended in women less than 60 years of age and within 10 years of menopause as: • it relieves vasomotor symptoms and other associated symptoms such as disturbed sleep, irritability, concentration problems and diminished quality of life which are related to the menopause. 102 (Level I), 125 (Level II-1) • it has a positive effect on mood disorders in women experiencing menopause related mood changes. The transdermal estrogen preparations may not show the same benefit.[146] (Level I) • it helps prevent and treat post-menopausal osteoporosis.[183] (Level I) • improves menopausal-specific quality of life scores (MsQOL) and global quality of life scores (Gqol).[246, 247, 247, 248] (Level I) • results in a more favourable global health index and a lesser all-cause mortality in women between the ages of 50 – 59 years.[224, 175] (Level I)
2.	Women with symptoms related to genitourinary syndrome of menopause are advised topical vaginal estrogen therapies as they are highly efficacious and carry minimal side effects.[101, 110, 148, 149, 150, 151] (Level 1)
3.	There are currently no recommendations for use of menopausal hormone therapy for: • prevention or treatment of sarcopenia in the menopause.[189] (Level I) • prevention or treatment of metabolic disorders in the menopause. 190,191 (Level I) • sole treatment of cognition or for reduction of Alzheimer's Disease in the menopause.[146, 195] (Level I), 196 (Level II-1) • sole treatment of the aging skin.[200] (Level II-2) • treatment of menopausal changes to hair, dentition, eyesight, hearing, smell, taste and voice.[201] (Level I), 202 (Level II), 203 (Level II-1), 204 (Level I)

Menopausal Hormone Therapy and Cancers

1.	Menopausal hormone therapy and breast cancer: • Estrogen only therapy for hysterectomised women (women without a uterus) is associated with a non-significant risk reduction or a very minimal increased risk of breast cancer which is relative to duration of estrogen use.[174,216 (Level I)] • Combined estrogen – progestogen therapy for non-hysterectomised women (women with a uterus) is associated with a small increased risk of breast cancer which is relative to duration of hormone use and type of progestogen used.[174,216 (Level I)] • Menopausal hormone therapy may be recommended for menopausal women with symptoms who have family history of breast cancer or carry a positive BRCA mutation.[220,221 (Level I)] • Menopausal hormone therapy is not advised for breast cancer survivors.[22(Level I), 226(Level III)] • Women with estrogen-receptor positive breast cancer (past or present) can use vaginal estrogen therapy for symptoms of genitourinary syndrome of menopause. There is no increased risk of breast cancer recurrence.[116 (Level II-1)]
2.	Women who have had a hysterectomy for cervical cancer may use menopausal hormone therapy (estrogen only) for treatment of menopausal symptoms.[229 (Level II-2), 230(Level I)]
3.	After endometrial cancer surgery, menopausal hormone therapy is not advised for treatment of menopausal symptoms due to fears of stimulating any remnant cancer cells.[233 (Level 1)]
4.	Menopausal hormone therapy (either estrogen only or estrogen progestogen combination) may be used for treatment of menopausal symptoms in women who have completed treatment for ovarian cancer.[174 (Level I)]

Duration of use of Menopausal Hormone Therapy (MHT)

1.	Post-menopausal women are allowed to continue menopausal hormone therapy without any mandatory time limit as long as an annual review with relevant investigations (see Section 5.11) and an annual benefit-risk assessment is carried out.[128 (Level I)]
2.	When long term menopausal hormone therapy (beyond 10 years) is considered, the low dose hormonal regime is advised.[88 (Level II-1), 101 (Level I)]
3.	Continued use of menopausal hormone therapy (beyond 10 years) is recommended in post-menopausal women with persistent vasomotor symptoms, to improve symptoms related to genitourinary syndrome of menopause, to increase bone density and to reduce fractures at all sites.[8 (Level II-3)]

Tibolone

1.	Post-menopausal women experiencing menopausal symptoms who are one year after their last period or after a surgical hysterectomy may be advised Tibolone.[256 (Level I)]
2.	Tibolone may also be advised in post-menopausal women: • who are unable to tolerate menopausal hormone therapy and for whom sexual health issues and libido are the main areas of concern.[256 (Level I)] • on continuous combined menopausal hormone therapy and want to transition into tibolone for long term use.[256 (Level I)] • with endometriosis or fibroids who need menopausal treatment, as tibolone has less effect on estrogen stimulated growths.[256 (Level I)]

Selective Estrogen Receptor Modulators (SERMs)

1.	Raloxifene hydrochloride is recommended for women with post-menopausal osteoporosis as it causes a 55% reduction in new vertebral fractures in women without prior fractures and a 31% reduction in women with prior fractures, when given over 3 years.[261 (Level I)]
2.	Raloxifene hydrochloride may be recommended for women with post-menopausal osteoporosis who are at a higher risk for breast cancer as it has been shown to decrease estrogen receptor breast cancer by 90% when given over 3 years.[262, 263 (Level I)]

Non-Hormonal Management of Menopause

1.	Herbal supplements such as isoflavones and phytoestrogens may be used for relief of vasomotor symptoms but have been found to be not more efficacious than placebo.[274, 275 (Level I), 276 (Level I)]
2.	1200 mgs of calcium supplements (a combination of dietary sources and supplements) is recommended due to its positive effect on bone mineral density and fracture risk reduction.[284 (Level II-3)]
3.	Adequate Vitamin D supplementation to achieve Vitamin D levels of more than 50 ng/mL is advised in order to maintain skeletal health and reduce the risk of fractures and falls.[285 (Level I)]
4.	Women experiencing menopausal symptoms may consider alternative therapy such as hypnotherapy, cognitive behavioral therapy, relaxation techniques, sleep hygiene and enforcing of positive attitudes to help ease anxiety, sleep and vasomotor symptoms.[289 (Level I)]

** **Menopausal Hormone Therapy (MHT)** is the new terminology to replace Hormone Replacement Therapy (HRT). Throughout this CPG, MHT would be used and is synonymous with HRT.

DEVELOPMENT OF GUIDELINES

The members of the Development Group (DG) for this CPG comprised of gynaecologists (both from the Ministry of Education and the private sector) who have been actively involved in the management of menopause in Malaysia, having run menopause clinics in their hospitals and published local papers on menopause health in Malaysia. They were aided by an endocrinologist from the private sector who specialises in post-menopausal osteoporosis and metabolic problems.

There was active involvement of allied health care professionals in the multidisciplinary review committee (RC) comprising of a family physician, an occupational health doctor, a pharmacist, a staff nurse and a doctor from East Malaysia so as to make this CPG as far reaching as possible. As this CPG is a combined effort with the Ministry of Health and Academy of Medicine, the representatives of each were present. Various ideas and suggestions were incorporated to complete this CPG.

There were 10 meetings carried out in the offices of the Obstetrical and Gynaecological Society of Malaysia in Kuala Lumpur. Two subsequent meetings were in the meeting rooms of Pantai Hospital Kuala Lumpur. As the pandemic struck, subsequent collaborations were through zoom.

A review of current and past literature was made using electronic databases including Medscape, OVID, PubMed and the Cochrane Data base of Systemic Reviews and Guidelines International Network (refer to Appendix 1 for Example of Search Strategy). Due to evolvement of hormone replacement therapy since 1990, the search covered literature published from 1990 – April 2021 on humans, specifically women and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 12th August 2018 to 23rd Feb 2020. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31st May 2021 to be included. Future CPG

updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

A total of 9 main clinical questions were developed under different sections (refer to Appendix 2 for Clinical Questions). Members of the working committee were assigned individual questions within these sections. All literature retrieved were appraised by at least two members of the working committee using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each meeting. All statements and recommendations formulated after that were agreed upon by the developmental group, the review committee and the external reviewers. Where evidence was insufficient, the recommendations were made through the consensus of the working committee, internal and external reviewers. Any differences in opinion were resolved consensually.

This CPG is based on the findings of systematic reviews, meta-analysis, relevant well conducted randomised clinical trials and cohort studies. Reference was made to the

- Clinical Practice Guidelines on Hormone Therapy During Menopause in Malaysian Women 2010,
- Clinical Practice Guidelines on Prevention of Cardiovascular Disease in Women 2016,
- Clinical Practice Guidelines on Management of Osteoporosis 2015,
- The 2017 hormone therapy position statement of the North American Menopause Society,
- International Menopause Society Recommendations on Women's Midlife Health and Menopause Hormone Therapy,
- Position statements from the British Menopause Society, Royal College of Obstetricians and Gynaecologists and Australian Menopause Society.

We looked into the national figures on prevalence and incidence of cardiovascular disease, osteoporosis and other long-term health issues. An in-depth review of all local data pertaining to menopause, its long-term effects and the use of conventional hormone therapy and alternative therapy was carried out. In view of Malaysia's multi ethnicity, the attitudes of the various cultures towards menopause and MHT use was studied in detail so as to understand the individual sensitivities.

The literature used in these guidelines were graded using the US / Canadian Preventive Service Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE. The writing of the CPG follows strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE II).

Key messages and recommendations were placed after each subheading to aid the user as quick reference. An algorithm has been designed to guide the user on management of a woman going through the menopause with or without the use of menopausal hormone therapy.

On completion, the draft of the CPG was reviewed by the two external reviewers. The draft was finally presented to the Technical Advisory Committee for the CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details of the CPG developmental methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence Based Clinical Practice Guidelines published in 2015. (available at http;//www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634)

OBJECTIVES

This clinical practice guideline has been drawn up to aid health care providers in:

- Increasing awareness about the importance of menopause and its long-term effects.
- Counselling a woman on the essential investigations that need to be carried out around the menopausal period.
- Advising a woman who is approaching menopause regarding lifestyle changes, including diet and exercise.

It would also provide evidence-based recommendations in

- Counselling and managing a woman on treatment with menopausal hormone therapy (MHT).
- Counselling and advising a woman on non-pharmacological treatments available in menopause.
- Identifying high-risk women, including those who menopause prematurely, and managing them appropriately for prevention of long-term health issues.

CLINICAL QUESTIONS

Refer to Appendix 2

TARGET POPULATION

- Women in the perimenopause, menopause and post menopause age group.
- Women who have been diagnosed with premature ovarian insufficiency (POI).

TARGET GROUP / USERS

This CPG is to guide those involved in the management of menopause at any healthcare level including:

- *Doctors.*
- *Allied health professionals.*
- *Trainees and medical students.*
- *Professional medical bodies.*
- *Pharmacists.*
- *Patients and their caregivers/ advocates*
- *Policy makers.*

HEALTH CARE SETTINGS

Primary, secondary and tertiary care settings

APPLICABILITY OF THE GUIDELINES AND RESOURCE IMPLICATIONS

Present health focus on an aging woman is on non-communicable diseases, osteoporosis, mental health and other age-related problems. This CPG aims to shift this focus to preventive and early detection strategies that could be put into place as a woman goes through menopause so as to decrease the health burden for the later years.

The initiation of menopausal hormone therapy should be carried out by specialists in the tertiary referral centres or health practitioners who are trained in menopause management. Continuation of treatment can be carried out in the district hospital setting using the algorithm set in this CPG.

Blood investigations, physical examinations including a pelvic examination and pap smear (if necessary), can be carried out at all levels of health care with the guidelines set in this CPG. Mammograms and bone mineral density examinations can be arranged periodically at district level hospitals or any health care facility.

The availability of various menopausal hormone therapy is also scarce and often unavailable at the peripheral health centres. With clear guidelines drawn with regards initiation, continuation and follow up of a woman whilst on MHT, it is hoped that the varied types of MHT become available for use.

IMPLEMENTATION OF THIS GUIDELINE

The successful implementation of this CPG is part of good clinical governance.

- Increasing public awareness towards menopause and its implications, management strategies and the use of MHT if necessary. This could be carried out by public forums in the various states of the countries. This could also be carried out by appropriate sites in face book, in various magazines, news and media. In view of the multi ethnicity of Malaysia, dispersing this message in the 3 main languages would reach a bigger fraction of the population.

- Making this CPG readily available in various medical society-based websites as listed above. This could be assessed by both the medical and public sector.

- Continuous medical educations (CME) programs either through workshops, meetings or seminars.

The Obstetrical and Gynaecological Society of Malaysia, the Malaysian Menopause Society and the Academy of Medicine (Chapter of Obstetrics and Gynaecology) would be working together towards implementing a Menopause Care Programme. This programme would involve an annually held weekend structured course with post course assessment test and a subsequent certificate as a “Menopause Care Practitioner”. This certification is to be reviewed every 3 years.

KEY MESSAGES ON MENOPAUSAL HORMONE THERAPY (MHT)

1.	Women going through the menopause should be thoroughly evaluated with a detailed history and a complete physical examination. Risk factor assessment for possible medical problems help in prevention and early diagnosis of menopause related health issues.
2.	Abnormal uterine bleeding in the perimenopause should always be investigated based on the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and causes which are not otherwise classified).[15] (Level III)
3.	Menopausal hormone therapy initiated within 10 years of the last menstrual period or in women younger than 60 years is an effective treatment for the following indications.[97] (Level I) • Women with moderate to severe vasomotor symptoms • Prevention and treatment of osteoporosis • Genitourinary Syndrome of Menopause (GSM)
4.	Women who initiate menopausal hormone therapy 10 years after menopause have a higher absolute risk of coronary heart disease, stroke, venous thromboembolism and dementia.[122] (Level I)
5.	There is presently no time limit to the duration of menopausal hormone therapy use. However, every woman on menopausal hormone therapy should have a risk/benefit assessment done on a yearly basis. Patient care should always be individualised for reasons of safety.[88] (Level II-1), 101 (Level I), 128 (Level I)
6.	In view of the long-term health sequelae in women with premature ovarian insufficiency, treatment with estrogen (and progestogen in women with intact uterus) is strongly recommended.[22] (Level1)

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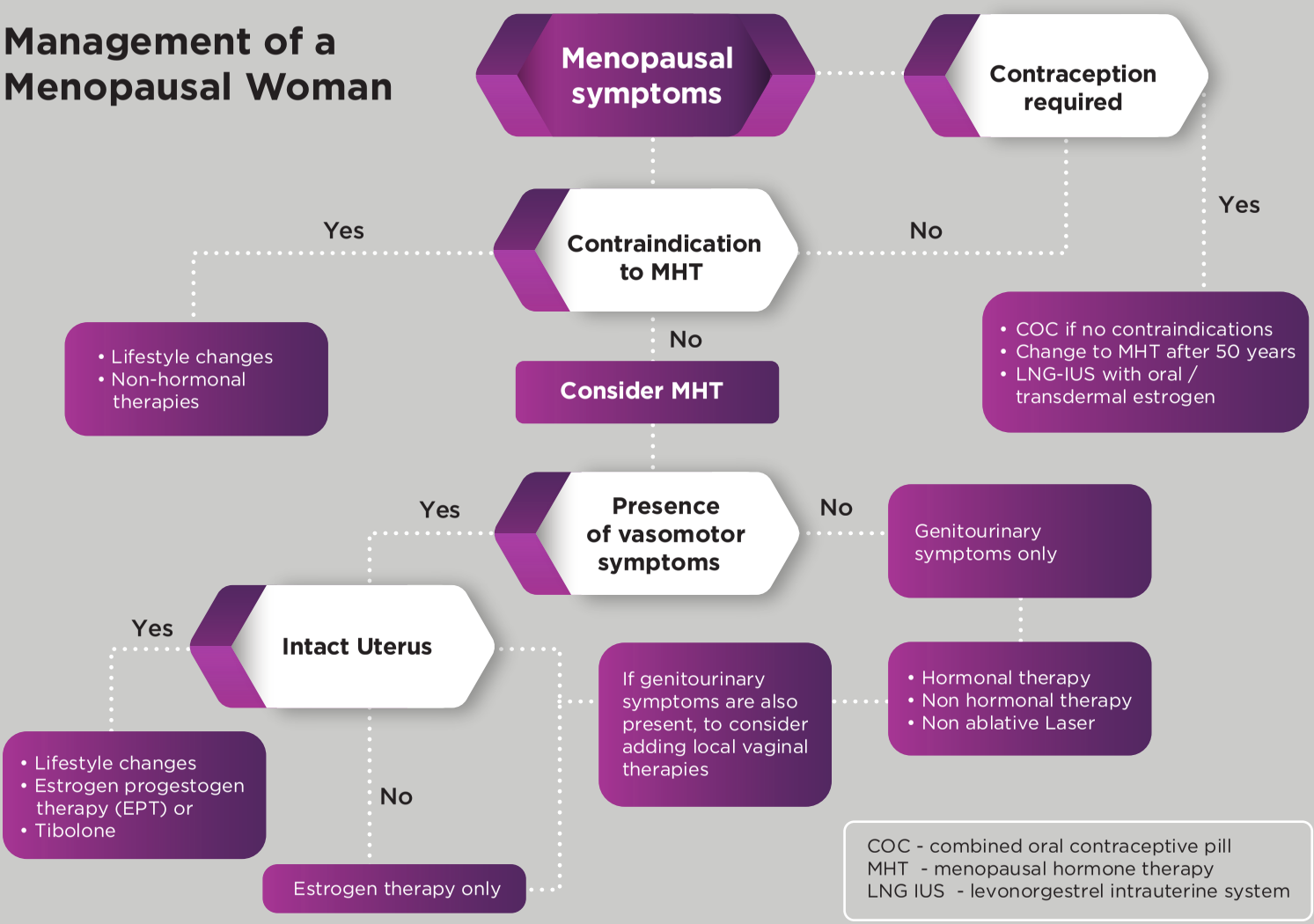
CLINICAL AUDIT INDICATORS

To assist in the implementation of the CPG, the following parameters are proposed as clinical audit indicators for quality management of menopause hormonal therapy use;

$$\text{Percentage of women developing coronary heart disease after menopausal hormone therapy use} = \frac{\text{Number of women developing coronary heart disease whilst on menopausal hormone therapy yearly}}{\text{Total number of women on menopausal hormone therapy yearly}} \times 100$$

$$\text{Percentage of women developing breast cancer after menopausal hormone therapy use} = \frac{\text{Number of women developing breast cancer whilst on menopausal hormone therapy yearly}}{\text{Total number of women on menopausal hormone therapy yearly}} \times 100$$

Management of a Menopausal Woman



A. Introduction

Menopause is a definite phase in a woman's life when her ovaries stop producing estrogen and her menstrual cycle stops. It also marks the end of her fertility. The diagnosis of menopause is made only after a woman has not had a period for twelve full months. As estrogen carries a protective effect on her organs, menopause then subjects a woman to various health problems and long-term morbidities.

In 2021, the average life expectancy of a Malaysian woman was 78.3 years.[1 (Level II-3)] As the average age of menopause in Malaysia is 50.7 years, one third or more of her life is now going to be spent in the post-menopause, a state of estrogen deficiency.[2 (Level II-3)]

While many women tend to be worried about the vasomotor symptoms and skin changes that are associated with the menopausal change, the long-term effects of menopause are more alarming. Estrogen protects a woman against metabolic diseases. Malaysian statistics show a high incidence of diabetes, high blood pressure and elevated cholesterol levels in the local post-menopausal cohort. The increased abdominal fat layer that occurs in women after menopause aggravates these medical health issues.[3 (Level II-3)]

Estrogen protects the heart and with menopause, the risk of cardiovascular disease increases. After the age of 55 years, the incidence of cardiovascular disease in both Malaysian men and women are on par, with coronary heart disease (CHD) being the leading cause of death for both sexes. Women unfortunately have an atypical presentation of CHD, which is usually precipitated by microvascular heart disease. This is further exacerbated by mental and emotional stress rather than with exertion, as in the man.

The risk of osteoporosis is doubled in post-menopausal women as compared to a man. By 2050, more than 50% of the world's hip fractures is projected to occur in Asia. Unfortunately, local data reveals a 20% mortality rate after a hip fracture with more than 40% of men and women always needing support or a walking frame for the rest of their lives.[4 (Level III)]

Malaysian women seldom talk of their symptoms related to the genitourinary syndrome of menopause (GSM) such as bladder incontinence, vaginal dryness, painful intercourse and bleeding during sex (sexual health issues). Many women suffer in silence and take it as an accepted part of growing old, affecting their self-confidence and partner relationships.

Mental health issues such as dementia and depression increase with age and women are more prone compared to men. Though depression can be multifactorial in origin, personal health issues with aging, loss of self-worth along with loneliness, increases its risk.[5] (Level II-3)

By 75 years of age, Malaysian statistics have shown that 1 in 4 men and women develop cancer, an important health burden especially with the increased life expectancy.[6] (Level II-3)

More than half the women going through menopause in Malaysia today will face 25 years of her life and more in an estrogen deficiency state. Many are unaware and unprepared of the full extent of their health challenges. Education of both health care workers and women approaching menopause regarding Identifying their health issues early, instigating lifestyle changes and regular monitoring of their health will definitely carry an overall beneficial effect.

Section 1: Definition of Menopause

1.1 Menopause in Malaysia

The average age of menopause in Malaysia is around 50.7 years.[2] (Level II-3) In 2000, a study from an urban menopause clinic showed that hot flushes (56%) and generalized tiredness (49%) were the predominant symptoms in urban menopausal women.[7] (Level II-3) More recently, a similar study in a similar urban setting found joint pains (73%) and fatigue (59.3%) to be most prevalent followed by vasomotor symptoms (55%).[8] (Level II-3) Malaysian women were also found to underestimate menopause-related problems and there was a lack in seeking treatment.[8,9] (Level II-3)

1.2 Stages of Menopause

The terminology used in the definition of menopause by the World Health Organization (WHO) in 1996 was endorsed by the International Menopause Society (IMS) in 1999.[10](Level III) Clinically, the following definitions are used:

- ***Natural menopause*** is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity. It is a retrospective diagnosis. A woman is said to be in the menopause, when she has not had any form of vaginal bleeding for 12 months after her last period, once pathological or physiological causes have been ruled out.

- ***Perimenopause*** includes the period immediately before menopause (when endocrinological, biological and clinical features of menopause begin) till one year after the last menstrual period.
- ***Menopausal transition*** starts when there is a variability in the menstrual cycle and lasts till the last menstrual period.
- ***The climacteric*** marks the transition from the reproductive phase to the non-reproductive phase in a woman. This phase is longer and extends from before the perimenopause to menopause.
- ***Premenopause*** which is often used ambiguously refers to the one or two years immediately before the menopause. This terminology is not encouraged.

In 2001, the Stages of Reproductive Aging Workshop (STRAW) proposed a staging system to depict the natural transition of a woman's life from the reproductive years to the time of menopause. This classification called the STRAW classification, used the menstrual cycle and hormonal measurements to define each stage of menopause.[11 (Level III)]

In 2012, this classification was updated based on new data taking into account follicle stimulating hormone (FSH) levels, antral follicle count (AFC), anti-müllerian hormone (AMH) levels and inhibin B levels.[11 (Level III)] *(Figure 1)*

The STRAW +10 classification is mainly used in research and clinical contexts when comparing studies of midlife women and facilitate clinical decision making.

Figure 1. The STRAW +10 Classification[11] (Levell-3)

	Menarche						FMP (0)			
Stage	-5	-4	-3	-3a	-2	-1	+1a	+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			Normal Low Low	Variable* Low Low	↑Variable* Low Low	↑>25 IU/L** Low Low	↑Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count 2-10mm			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 pituitary standard

1.	The average age of menopause in Malaysia is 50.7 years.[2] (Level II-3)
2.	A woman is said to be in the menopause when she has not had a period for 12 months without any preceding pathological or physiological cause.[10] (Level III)
3.	The perimenopause is the period immediately before menopause till one year after the last menstrual period.[10] (Level III)

1.3 The Perimenopause

Perimenopause is the phase before menopause when the endocrinological, biological and clinical changes of menopause begin till one year after the last menstrual period. During this phase, erratic peaks in serum estradiol and serum progesterone can bring about a wide variation in cycles and flow.[12] (Level II-3)

Perimenopausal women may exhibit more symptoms than their post-menopausal counterparts due to the fluctuating estrogen levels. The range of symptoms may vary and may be interrelated. Symptoms are usually exaggerated the further away the woman is from her last period with the symptoms lessening once the period starts again. Fortunately, not all women experience severe symptoms. *Table 1* lists the more common symptoms experienced during the perimenopause phase.

Table 1: The Perimenopause Symptoms[13 (Level II-3)]

Symptoms of Perimenopause
A change in the menstrual cycle and flow
Abdominal bloating
Headaches
Breast swelling and tenderness
Mood swings
Anxiety
Depressive symptoms
Memory problems
Skin dryness or itchiness
Myalgia, arthralgia, joint pains
Disturbed sleep patterns
Weight gain (mainly over the midriff)
Hair loss
Vasomotor symptoms (VMS) which include hot flushes and night sweats
Reduced sexual function

Diagnosis of perimenopause is purely based on clinical signs and symptoms of the menopause. Measurements of serum follicle-stimulating hormones (FSH) levels and estradiol levels are unnecessary at this stage.

Perimenopause brings about altered menstrual cycles. The cycles may be initially shorter followed by longer intervals. The flow may vary from prolonged spotting to heavy periods with clots. A woman is said to be in the menopause when she does not get a period for one whole year.

As ovulation can be unpredictable in the perimenopause, contraception is still required till one year after the last menstrual period.[14 (Level I)]

Abnormal uterine bleeding (AUB) during the perimenopause should always be investigated, based on the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified).[15 (Level III)]

Sexually active women presenting with AUB, should have a vaginal examination, a pap smear and a transvaginal pelvic ultrasound carried out to exclude pathology in the cervix, uterus and ovaries. Pregnancy should also be ruled out.

If a vaginal examination cannot be done, a pelvic ultrasound on a full bladder would suffice to rule out pelvic pathology. Appropriate blood tests such as a full blood count, thyroid profile and coagulation profile may become necessary. Other invasive investigations such as an examination under anaesthesia (EUA), endometrial biopsy or hysteroscopy are optional procedures based on the findings of the above examination.[15 (Level III)]

Treatment options for abnormal bleeding in the perimenopause include non-hormonal medical treatments such as non-steroidal anti-inflammatory drugs and antifibrinolytics, the combined oral contraceptive pill or menopausal hormone therapy and the levonorgestrel intrauterine system (LNG-IUS) for endometrial protection. [14,16 (Level I)] This is further discussed in *Section 6.1.* Hormonal therapy such as the combined oral contraceptive or menopausal hormone therapy can only be given in the absence of contraindications.*(Section 5.2)*

Abdominal bloating is common in the perimenopause as the decreasing hormones cause changes in the intestinal motility. This may lead to food sensitivities and intolerance. Any unexplained changes in the gastrointestinal system should always be investigated.

The fluctuating estrogen levels in the perimenopause may increase body weight especially around the abdominal area which in turn increases metabolic problems. Thyroid abnormalities are common in the perimenopause and should always be ruled out.[13 (Level II-3)]

The other symptoms of the perimenopause are discussed in *Section 2.*

The perimenopause is the appropriate time to counsel a woman with regards to her present health status and long-term consequences of menopause. Lifestyle modifications in diet and exercise should be discussed. Breast screening and bone density measurement (in high-risk individuals) may be carried out as part of the screening. *See Section 3 (Clinical Assessment and Investigations).*

Recommendation 1	
1.	Women experiencing abnormal uterine bleeding in the perimenopause should always be investigated based on the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified).[15] (Level 111)
2.	Clinical investigations for a woman with abnormal uterine bleeding include a vaginal examination, a pap smear (in sexually active women) and a pelvic ultrasound to rule out local pelvic pathology. If a vaginal examination cannot be carried out, a pelvic ultrasound on a full bladder would suffice.
3.	Blood investigations for anemia, thyroid dysfunction and coagulation disorders (if necessary) are advised.[5] (Level 111)

1.4 Premature Ovarian Insufficiency (POI)

Premature ovarian insufficiency (POI) is the cessation of ovarian function below the age of 40 years. It affects 1% of the female population.[17] (Level II-3) The most common cause is idiopathic, however it may also result from medical diseases or surgical intervention. Ten percent of women with POI have a genetic predisposition (Turner's syndrome 45XO and Fragile X).[18, 19] (Level I)

The two most clinically important autoimmune conditions associated with POI are Addison's disease and hypothyroidism. Other rare causes include Type 1 diabetes mellitus (T1DM), coeliac disease, antiphospholipid syndrome, infection (mumps), metabolic, environmental factors and iatrogenic causes. *(Table 2)*[18] (Level I)

Given the diverse causes of POI, the clinical presentation varies. Twenty percent of women with POI may present with primary amenorrhea and 10% will present with secondary amenorrhea. Women who present with primary amenorrhea do not have menopausal symptoms. Women with secondary amenorrhea usually present with more severe menopausal symptoms compared to women undergoing natural menopause. Psychological symptoms including depression, anxiety, negative self-image and sexual dysfunction may manifest with the onset of period abnormalities.

Women with POI are at risk of long-term consequences of estrogen deficiency, especially osteoporosis,[20 (Level I)] premature coronary artery disease, cardiovascular disease and dementia.[18 (Level I)]

Diagnosis of POI is based on serum follicle-stimulating hormones (FSH) of over 40IU/l at 4 to 6 weeks apart in women presenting with 4 months of amenorrhea or irregular cycles. Anti-Mullerian Hormone (AMH) levels may be considered as a diagnostic tool, as it is highly sensitive to ovarian ageing and further excludes uncertainties associated with the intra and inter cycle variability.[21 (Level II-3)]

Other investigations include:

- Karyotyping to exclude Turner's or other chromosomal abnormalities. Permutation studies to exclude Fragile X syndrome is recommended in normal karyotypes.
- Autoimmune screen to exclude anti-thyroid peroxidase antibody, anti-adrenal antibody and coeliac serology.
- Ultrasound assessment of the pelvis may be performed in establishing the diagnosis of POI other than to exclude pregnancy.

In view of the long-term health sequelae with POI, hormonal treatment with estrogen and progestogen (in the absence of contraindications) is strongly recommended. Women with POI would require higher doses of estrogen than the dose available in MHT. The aim is to achieve approximately 100 pg/ml of estradiol / day, which is necessary for the normal functioning of the organs. Women with POI still have a 5-15 % chance of getting pregnant due to intermittent ovarian activity.[22 (Level1)]

In women without contraindications to its use, the low dose combined oral contraceptive (COC) is the ideal hormone replacement, acts as a contraceptive and is recommended until the age of natural menopause (50 years).[20 (Level1)] Thereafter, if hormones are still required, menopausal hormone therapy is advised.

MHT may be used as an alternative to COC in women with POI, however additional protection for contraception is required till the age of 50 years.[20 (Level1)]

The diagnosis of POI may bring about depression and other mental health issues. A psychological consult is advised along with the regular gynaecological visits.[18, 22 (Level I)]

Table 2: Causes of POI [18 (Level I)]

Causes of POI	
Idiopathic (most common)	
Genetic causes (10%)	Turner's syndrome
	Fragile X
Autoimmune causes (20%)	Autoimmune hypothyroidism
	Addison's disease
	Type 1 diabetes mellitus (DM)
	Coeliac disease
Inborn errors of metabolism	
Environmental causes	Smoking
Iatrogenic causes	Post chemotherapy
	Radiotherapy
Surgical causes	Removal of both ovaries / removal of uterus and both ovaries

1.	Premature ovarian insufficiency (POI) is cessation of ovarian function below the age of 40 years and affects 1 % of the female population.[17 (Level II-3)]
2.	Diagnosis of POI is based on Follicular Stimulating Hormone (FSH) levels of over 40 IU/l 4- 6 weeks apart in women with 4 months of amenorrhea or irregular cycles.[21 (Level II-3)]
3.	In view of the long-term health sequelae in women with premature ovarian insufficiency, treatment with estrogen (and progestogen in women with intact uterus) is strongly recommended.[22 (Level1)]

Recommendation 2	
1.	Women with premature ovarian insufficiency are strongly recommended treatment with estrogen (and progestogen in women with intact uterus) to prevent long term health sequelae such as osteoporosis, premature coronary artery disease, cardiovascular disease and dementia.[18, 20, 22 (Level I)]
2.	The low dose combined oral contraceptive pill (COC) is recommended for women with premature ovarian insufficiency and is advised till the age of menopause (50 years). It acts both as a hormone replacement and a contraceptive.[20 (Level1)]
3.	Menopausal hormone therapy (MHT) may be used as an alternative to the combined oral contraceptive (COC) pill in women with premature ovarian insufficiency. Additional measures should be advised if contraception is required.[20 (Level1)]

Section 2: Symptoms of Menopause

2.1 Vasomotor symptoms (VMS)

Vasomotor symptoms (VMS) which consists of both hot flushes and night sweats are the cardinal symptoms which happen around menopause. Hot flushes are sudden waves of heat over the upper body and face lasting 1-2 minutes, which is then followed by sweating. Night sweats are episodes of sweating that happen in the night which result in poor sleep. VMS symptoms do not occur in all women and its intensity may also vary from individual to individual.

Women with frequent vasomotor symptoms have been shown to have a twofold increase in developing coronary heart disease (CHD) over the next 14 years irrespective of their age, menopause status, lifestyle, and other chronic disease risk factors when compared to women with no symptoms.[23 (Level II-3)] These women have also been shown to have poorer endothelial function, more aortic calcification and greater intima thickness than women without vasomotor symptoms.[24 (Level II-3)]

Two different studies set in an urban population in Malaysia have shown that hot flushes affect more than 50% of Malaysian women which then led to a lowered quality of life.[7, 8 (Level II-3)]

The Women's Health Initiative (WHI) trials showed that women with more frequent and intense VMS and night sweats experienced an almost two-fold increase in hip fractures in the subsequent years of follow up.[25 (Level I)]

Presence of objective VMS has also been shown to correlate significantly with memory loss, alterations in brain function during rest and is associated with white matter hyper intensive areas in the brain.[26 (Level I)]

Night flushes and sweats can interrupt sleep and change sleep patterns. This in turn leads to increased tiredness and mood changes. Though not vasomotor in origin, joint pains, lethargy and fatigue were other common symptoms experienced by Malaysian women during the transition.[7, 8 (Level II-3)]

1.	Hot flushes affect more than 50% of women in Malaysia.[7, 8 (Level II-3)]
2.	Women with frequent hot flushes have been shown to have a twofold increase in developing coronary heart disease over the next 14 years irrespective of their age, menopause status, lifestyle, and other chronic disease risk factors when compared to women with no symptoms.[23 (Level II-3)]
3.	Women with intense hot flushes and night sweats experience a twofold increase in developing hip fractures in the following years. [25 (Level I)]

2.2 Mood Disorders

Fluctuating estrogen and progesterone levels during the menopause transition increase the risk of mood disorders and depression. The strongest predictors of mood disorders during this phase are prior history of depression, history of postpartum depression and severe premenstrual symptoms.[27 (Level II-3)]

Symptoms can range from irritability, palpitations, poor sleep, crying spells, anxiety and feelings of low mood. The intensity of these symptoms may lessen well into post menopause.

A study on about 4000 women in the perimenopausal age group in Malaysia showed a 54% prevalence rate of depressive symptoms. These symptoms were higher in the perimenopausal group compared to women who were post-menopausal.[28 (Level II-3)]

1.	Fluctuating estrogen and progesterone levels during the menopause transition increase the risk of mood disorders and depression.[27] (Level II-3)
2.	The strongest predictor for mood disorders during the menopause is prior history of depression, history of post-partum depression and severe premenstrual symptoms.[27] (Level II-3)

2.3 Genitourinary Syndrome of Menopause (GSM)

Genitourinary syndrome of menopause (GSM) replaces the term vulvovaginal atrophy or atrophic vaginitis. The symptoms of GSM include vaginal dryness, painful sex, sexual dysfunction, bladder and urethral symptoms, frequent urinary tract infections along with vaginal burning, itching and irritation.[29] (Level I)

Decreasing estrogen levels alter the normal multi-layered thick vaginal epithelium rich in blood vessels and glycogen to a thin, dry epithelium. There is concomitant change in vaginal flora, loss of lactobacilli and an increase in pH which then leads to an increase in vaginal and urinary infections.[29] (Level I)

These vaginal changes can lead to vaginal dryness (33%) and sexual dysfunction (88%) within two years of menopause.[30] (Level II-3) The Pan Asian Revive Study (a questionnaire-based study which also involved Malaysian women between the ages of 45 and 75 years) showed that 55% of Asian women suffered from vaginal dryness, 44% had dyspareunia, 37% had vaginal irritation and 6% of women experienced bleeding after sexual intercourse. Half of these women felt that these problems were part of aging and that seeking advice from the health care providers concerning these symptoms was not necessary.[31] (Level II-3)

1.	Genitourinary syndrome of menopause is a very significant symptom of the menopause which causes vaginal dryness, painful sex, sexual dysfunction, bladder and urethral symptoms, frequent urinary tract infections along with vaginal burning, itching and irritation.[29] (Level I)
2.	Decreasing estrogen levels alter the previously thick vaginal epithelium rich in blood vessels and glycogen into a thin dry epithelium; with concomitant changes in vaginal flora, loss of lactobacilli and an increase in pH.[29] (Level I)

2.4 Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) is the leading cause of death in Malaysian women.[32 (Level I)] After a cardiovascular event, women tend to have poorer long-term outcomes and quality of life when compared to a man.[33 (Level II-3)]

A woman's risk for CVD increases dramatically at menopause due to the following factors:[34, 35 (Level II-3), 36, 37,38,39 (Level I)]

- Effect of increasing age.
- Loss of estrogen.
- Changes in body fat distribution and storage.
- Decrease in physical activity.
- Increase in blood pressure.
- Worsening lipid levels.
- Worsening glucose tolerance and insulin resistance.

The incidence of coronary heart disease is 2-3 times higher in post-menopausal women than in pre-menopausal women.[35 (Level II-3)] This is likely due to increased microvascular disease and carotid intima media thickness (a marker of subclinical atherosclerosis), which occur in the menopause.[40 (Level II-3)]

Women often present with varied, unrelated symptoms to the emergency department which then result in a delayed diagnosis.[41 (Level I)] While angina pectoris is more common in women compared to men, non-chest related symptoms such as fatigue, epigastric pain and shortness of breath may actually be related to a cardiac event.[42 (Level I)]

Reduction of modifiable risk factors is the most effective strategy for prevention of CVD. The INTERHEART study, a global case-controlled study which examined modifiable risk factors across many populations, determined that in women, 94% of CVD risk could be attributed to modifiable factors such as diabetes mellitus (OR 2.37), hypertension (OR 1.91), abdominal obesity (OR 1.62), current smoking (OR 2.87) and psychosocial stress (OR 2.67).[43(Level II-3)]

1.	Cardiovascular death is the leading cause of death in women in Malaysia.[32 (Level I)]
2.	A woman's risk of cardiovascular disease increases with age, loss of estrogen, changes in body fat distribution, decrease in physical activity and an increase in blood pressure, lipids and glucose levels. [34, 35 (Level II-3), 36, 37, 38, 39 (Level I)]
3.	The incidence of coronary heart disease is 2-3 times more in post-menopausal women than in premenopausal women.[35 (Level II-3)]
4.	Women often present with varied, unrelated symptoms to the emergency department which lead to delayed diagnosis.[41 (Level I)]
5.	Reduction of modifiable risk factors such as diabetes mellitus, hypertension, abdominal obesity, current smoking and psychosocial stress is the most effective strategy for prevention of cardiovascular disease.[43(Level II-3)]

2.5 Stroke

Stroke is one of the leading causes of morbidity and mortality worldwide. Women account for 60% of all stroke events. Although age adjusted stroke risk is higher in men than women, more stroke events occur in women because of their longer life expectancy and the higher incidence of strokes at a later age.[44,45 (Level I)]

The risk of ischemic stroke increases with

- Menopause. The risk of stroke doubles in women after 10 years of menopause. Estradiol has been shown to provide a neuroprotective effect in premenopausal women.[46 (Level II-1)]
- Other risk factors such as hypertension, diabetes, obesity (increased waist – hip ratio), dyslipidaemia and smoking.[47 (Level I)]

The Malaysian Stroke Registry (2009- 2016) census gives the mean age of stroke at 62.5 years. Sixty percent of stroke victims were more than 60 years, 26% were between 50 – 59 years with 13.6 % below the age of 49 years. The risk of stroke was higher in males in all age groups till the age of 70 years when women predominated, a factor that could be attributed to the increased

life expectancy of women. Hypertension (67%), diabetes (39.6%), cigarette smoking (25.2%) and hyperlipidaemia (23%) were the other commonest risk factors.[48 (Level II-3)]

1.	The risk of stroke doubles after 10 years of menopause.[46 (Level II-1)]
2.	Other risk factors that can contribute to stroke are hypertension, diabetes, obesity, dyslipidemia and smoking.

2.6 Venous thromboembolism (VTE)

VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The incidence of VTE is 1 per 1000 person years amongst post-menopausal women with a fatality rate of 10%. Seventy percent of cases of VTE are hospital acquired.[49, 50 (Level I)]

The risk of VTE in Asia is increasing mainly due to increased life expectancy, obesity, and cancer.[51(Level I)] Genetic factors such as Factor V Leiden mutation and deficiencies of Protein C, S, and anti-thrombin are other factors that increase the risk of VTE.

Women who menopause early (POI) have a lesser risk of VTE when compared to women who menopause around 50 years. In view of this, hormone replacement remains the treatment of choice in these women, without the additional fear of possible VTE. [52 (Level II-1)]

Women with late menopause have a higher risk of VTE. Each year's delay increases the risk of VTE by 7%. Having more than two children increases the risk of VTE by 2-fold when compared to women with lesser children. The combination of late menopause and high parity confers a threefold increase in VTE risk.[53 (Level II-3)]

1.	The incidence of venous thromboembolism is 1 per 1000 person years amongst post-menopausal women with a fatality rate of 10%. [49, 50 (Level I)]
2.	Women who menopause early have a lesser risk of venous thromboembolism (VTE) compared to women who menopause late. Each year's delay in menopause, increases the risk the risk of VTE by 7%.[53 (Level II-3)]

2.7 Osteoporosis

Bone mineral density (BMD) peaks during the third decade of life and declines with advancing age. The reduction in estrogen levels at menopause causes an accelerated rate of bone loss.

Women lose about 50% of their trabecular bone and 30% of their cortical bone during the course of their lifetime, about half of which is lost during the first 10 years after the menopause.[54,55 (Level I)]

Accelerated bone loss starts during the late perimenopause and continues during the early postmenopausal years. The annual rate of loss is 1.8–2.3% at the spine and 1.0–1.4% at the hip.[56 (Level II-3)] Five years into menopause, there is an estimated 7–10% decline in the spine BMD and 5–7% decline in the hip BMD. This loss is estimated to increase fracture risk by 50–100%.[57 (Level I)]

Body weight is an important determinant of the rate of BMD loss. Women with low body weight have a faster rate of BMD loss.[56 (Level II-3)]. Ethnicity is not found to influence the rate of bone loss.[58 (Level I)] *(see Table 3)*

Perimenopausal women with low body mass index (BMI) should be ideally screened for osteoporosis. The OSTA (Osteoporosis Self-Assessment Tool for Asians) may be used *(see Appendix 4).*

Table 3: Risk factors for Osteoporosis [58 (Level I)]

Non-Modifiable Risk Factors	Modifiable Risk Factors
Advancing age	Low calcium and or Vitamin D intake
Female gender	Sedentary lifestyle
Premature Ovarian Insufficiency	Cigarette smoking
Cessation of periods before 45 years (including surgical menopause)	Excessive alcohol intake (> 3 units / day)
Personal history of non-traumatic fracture as an adult	Excessive caffeine intake (> 3 drinks / day)
Family history of osteoporotic hip fracture in first degree relative	Low body mass index (< 19 kg / m2)
	Recurrent falls

1.	Women lose about 50% of their trabecular bone and 30% of their cortical bone during the course of their lifetime, about half of which is lost during the first 10 years after the menopause.[54,55] (Level I)
2.	An estimated 7–10% decline in the spine bone mineral density (BMD) and 5–7% decline in the hip BMD which occurs after 5 years of menopause then increases fracture risk by 50–100%.[57] (Level I)

2.8 Sarcopenia

Sarcopenia is an age-related involuntary loss of skeletal muscle mass and strength. From the 4th decade of life, skeletal muscle mass and strength decline in a linear fashion, with up to 50% of muscle mass being lost by the 8th decade of life.[59] (Level II-3)

Potential causes of sarcopenia include age-related hormonal changes, environmental factors (low levels of physical activity, reduced protein and calorie intake) and increased oxidative stress. The decrease in muscle mass with aging results from the bulk loss of Type 2 (fast twitch) motor units,[60] (Level II-1) with a marked infiltration of fibrous and adipose tissue into the skeletal muscle.[61] (Level I)

Loss of Type 2 muscle causes disability and problems with certain movements, such as rising from a chair, climbing steps or regaining posture after a disturbance in balance.

Sarcopenia is an age related, involuntary loss of skeletal muscle and strength; up to 50% of muscle mass can be lost by 80 years of age.[59] (Level II-3)

2.9 Metabolic Syndrome, Weight & Diabetes

The prevalence of metabolic syndrome (MetS) increases after menopause.[62 (Level I)] MetS consists of abdominal obesity, insulin resistance/glucose dysregulation, dyslipidaemia and hypertension.[63 (Level I)]

After menopause, there can be an average weight gain of 2.0-2.5 kg over 3 years. [64 (Level I)] Weight gain and obesity are the main drivers of the increased prevalence of MetS in postmenopausal women.[65 (Level II-3)]

The increase in visceral fat (especially around the abdomen), which can start as early as 3-4 years before menopause, along with changes in body composition and reduction in muscle mass, further affect metabolic health.[66 (Level I)]

Metabolic Syndrome (MetS) encompasses abdominal obesity, insulin resistance / glucose dysregulation, dyslipidemia and hypertension. MetS increases after menopause.[62, 63 (Level I)]

2.10 Cognition

Estrogen has been shown to have a positive effect on long-term cognition. Women who are older at the time of menopause have better cognitive function, particularly in verbal memory,[67 (Level II-3)] whilst women with POI have been shown to have poorer long-term effects on cognitive function.[68 (Level II-3)]

Cardiovascular risk factors identified at midlife are shown to be able to predict risk of cognitive decline and dementia later in life. The presence of diabetes, hypertension, smoking and elevated cholesterol levels (dyslipidaemia) during the forties doubled the risk of developing dementia when older.[69 (Level II-3)]

Estrogen has a positive effect on long term cognition.[67 (Level II-3)]

2.11 Skin

Total collagen declines an average of 2.1% per post-menopausal year over a period of 15 years; however some studies have shown a 30% loss of both Type I and II collagen in 5 years.[70 (Level1)]

Skin changes associated with loss of estrogen are [71(Level I)]

- Oily skin due to an increase in sebum production.
- Sagging skin and wrinkles due to change in fat distribution.
- Elastosis due to lesser production of collagen and elastin.
- Thinning epidermis due to loss of blood capillaries and a reduction in the barrier function of the epidermis. This can lead to dryness and itchiness often experienced by menopausal women.
- Hyperpigmentation or age spots due to increase in melanin synthesis as a result of hormonal imbalance.

Up to thirty percent of skin collagen may be lost within the first 5 years of menopause.[70 (Level I)]

2.12 Hair, Dentition, and Special Senses

2.12.1 Hair

With the change in the androgen: estrogen ratio, male pattern baldness may appear alongside darker hair seen over the chin, upper lip and chest. Scalp hair is also lesser and thinner.[72 (Level II-3)]

Thinning of scalp hair, male pattern baldness along with darker hair over the chin, upper lip and chest can occur with the menopause.[72 (Level II-3)]

2.12.2 Dentition

During menopause, gums become more susceptible to plaque build-up leading to a higher risk of gingivitis and advanced periodontis.[73] (Level I)

The jaw bone also goes through bone loss leading to loosening of teeth and mandibular dysfunction.[74] (Level II-3) Other changes include mouth dryness due to lesser saliva secretion, gingival atrophy, oral ulcerations, oral candidiasis, sensations of painful mouth and burning mouth syndrome.[75] (Level I)

Menopausal changes to the dentition include increased risk of gum disease, bone loss at the jaw leading to loosening of the teeth and mandibular dysfunction along with changes associated with mouth dryness.[73,75] (Level 1), 74 (Level II-3)

2.12.3 Vision

Dry eyes is a common problem with menopause and is caused by an inflammatory process within the lacrimal glands.[76] (Level I) Cataracts are also more prevalent in post-menopausal women as estrogen confers an anti-oxidative protection against cataractogenesis.[77] (Level I)

Surgical menopause in women before the age of 45 years carries an increased incidence of macular degeneration compared to women who undergo menopause naturally after 45 years (RR 3.8; 95% CI, 1.1-12.6).[78] (Level II-1)

Dry eyes and cataracts are prevalent in postmenopausal women.[76, 77] (Level I)

2.12.4 Voice

Menopausal women have more throat clearing episodes and mouth dryness compared to premenopausal women. Higher androgen levels may lead to hoarseness of the voice.[79] (Level II-1)

Mouth dryness and hoarseness of voice may occur in the menopause.[79] (Level II-1)

2.12.5 Hearing

The estrogen hormone may have a positive influence on hearing. A prospective 10-year longitudinal study of perimenopausal women found a continuous decline in hearing at all frequencies with age, with a higher rate of decline during the menopause period.[80](Level II-3)

A higher rate of decline of hearing occurs during the menopause period.[80](Level II-3)

2.12.6 Smell

Ageing is accompanied by olfactory loss and hyposmia or anosmia; women seem to be affected more strongly than men.[81] (Level II-3)

With ageing, women are more affected by olfactory loss and sense of smell than men. [81] (Level II-3)

2.12.7 Taste

Menopause can change taste and neuronal function. This is caused by reduction in saliva production, dysesthesia and atrophic gingivitis.[82] (Level II-1)

Menopausal women may experience a change in taste and neuronal function.[82] (Level II-1)

2.13 Quality of Life (QoL)

Several studies have demonstrated an association between menopausal symptoms and a lowered quality of life.[83, 84, 85 (Level II-3)]

Depression and anxiety have been shown to have the largest effect on mental Health-Related Quality of Life (HRQoL) scores whilst joint stiffness and heart palpitations are the main concerns in the physical HRQoL scores.[86 (Level II-3)]

Menopause affects both mental and physical Health Related Quality of Life scores. [86 (Level II-3)]

Section 3: Clinical Assessment and Investigations

Women going through the menopause should be thoroughly evaluated with a detailed history and a complete physical examination. This would be considered Good Clinical Practice (GCP). Risk factor assessment for possible medical problems help in prevention and early diagnosis. It also provides a baseline for assessment if menopausal hormone therapy is considered.[87 (Level I), 88 (Level II-1)]

Table 4: Detailed History *(GCP)* [87 (Level I), 88 (Level II-1)]

Personal history, including menopausal symptoms (if any).
Menopausal Questionnaire may be used. (Appendix 3)
Obstetric history
Gynaecological history
Menstrual and sexual history
Previous medical history
Previous surgical history
History of allergies and drug sensitivities including sensitivities to hormones

History of blood clotting problems
Family history especially of hormone related cancers, cardiovascular disease, clotting problems and osteoporosis
Social history including history of smoking, vaping and alcohol intake
Lifestyle history including stress, dietary history and exercise history

Table 5: General Examination *(GCP)*

Blood pressure
BMI
Breast examination
Abdominal examination - to rule out pelvic masses
Vaginal examination (if applicable)*. To rule out infections, cervical lesions, pelvic masses and to assess pelvic floor

Table 6: Recommended Investigations *(GCP)*

Full blood count
Liver and renal function tests
Fasting blood glucose and fasting serum lipids
Pap smear (if applicable) *
Breast screening using ultrasound and / or mammography
Bone mineral density (if needed)
OSTA can also be used to identify those at risk for osteoporosis *(Appendix 4)*

*Vaginal examinations and pap smears are carried out only in women who are / have been sexually active.

Blood tests for FSH (Follicular Stimulating Hormone) should not be routinely considered when diagnosing menopause in women aged over 45 years.[88 (Level II-1)]

The breast ultrasound is complimentary to the mammogram especially in younger women who have dense breast tissue.

Women going through the menopause should be thoroughly evaluated with a detailed history and a complete physical examination. Risk factor assessment for possible medical problems help in prevention and early diagnosis of menopause related health issues.

Section 4: Lifestyle Changes During Menopause

Practicing a healthy lifestyle during the menopause is encouraged. This involves eating healthy, maintaining an ideal weight, cessation of smoking, reducing alcohol consumption, and optimising blood pressure and glucose levels.[90, 91(Level I)]

- Dietary changes should include a reduction in polyunsaturated fats, trans fats, salt and sugar. Hot flushes may be exaggerated with excessive coffee and spicy food intake.[92 (Level I)]

- Regular exercise for 30 minutes at least five days a week is encouraged.[90, 91(Level I)] Regular physical activity can decrease physical and emotional issues associated with menopause.[93(Level II-1)] Activities such as yoga, tai chi, aerobics, walking, swimming, and strength training may also help reduce the severity of menopausal symptoms.[94 (Level I)]

- A sound sleep of 6-9 hours every night not only improves self-rated quality of life but lowers depression scores. Sleep strongly influences many aspects of health (physical, cognitive, and emotional) which in turn improves general health.[90, 91, 95 (Level I)]

- Women are usually stressed about how menopause would affect their lives. Strategies that induce relaxation and inner tranquility such as meditation, traditional massages, acupuncture and simple breathing exercises help reduce this stress which in turn helps reduce menopausal symptoms.[96 (Level I)]

- Support group programs have a significant effect on decreasing physical, psychological, and social changes induced by the menopause. Participation of other family members, especially spouses, in physical and mental health programs, can contribute to a greater improvement of women's QoL.[96 (Level I)]

Table 7: Lifestyle changes that are Important in the Menopause *(CGP)*

1.	Maintaining a healthy weight
2.	Stop smoking or vaping
3.	Cutting down spicy food and excessive coffee intake
4.	Minimising polyunsaturated fats, trans fats, salt, and sugar
5.	Minimising alcohol
6.	Blood pressure control
7.	Regular exercise 5 days a week; 30 minutes each time
8.	Sleeping soundly for 6-9 hours every night
9.	Stress reduction
10.	Support group programs (in particular spousal support)

Women going through the menopause should be encouraged to practice lifestyle changes which include healthy eating, regular exercises, sleeping soundly, relaxation therapies and support group involvement.

Section 5: Menopausal Hormone Therapy

5.1 Introduction

The terminology "Menopausal hormone therapy (MHT) has replaced "Hormone replacement therapy (HRT)"

MHT is recommended to women who experience menopausal symptoms that affect their quality of life. It is also advised for women to prevent or manage chronic conditions that may occur with menopause.

Benefits of MHT outweigh risks when given to healthy symptomatic women who are less than 60 years or within 10 years of onset of menopause.[97] (Level I)

MHT is the most effective treatment for VMS and GSM. It is the only known treatment that has been shown to prevent bone loss and reduce fractures.[97] (Level I)

The Women's Health Initiative (WHI) study was a large double blinded, placebo controlled, randomised study that assessed the effect of hormones on the health of 160,000 women between the ages of 50 – 79 years. The study had two arms; one arm assessed the effect of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) in women with a uterus whilst the other arm assessed the effect of CEE alone in women without a uterus. In 2002 and 2004, both arms of the (WHI) study was prematurely stopped. The study with women on the combined therapy of CEE and MPA was halted at 5.6 years due to an increased risk of breast cancer and when other overall risks exceeded benefits. The study with women on the estrogen only arm was halted at 7.2 years due to an increased risk of stroke.[98] (Level I)

Post WHI, further breakdown of the data has shown that the benefits and risks of MHT vary with the woman's age, time since menopause, underlying health conditions, type of MHT used and delivery methods. The "timing hypothesis" showed that the risks with MHT use was lower in women closer to menopause onset than in those distant from the transition.

In 2017, a cumulative observational follow of the WHI study revealed that women on hormone therapy, either CEE and MPA (non-hysterectomised women) or CEE alone (hysterectomised women), showed no increased risk of all-cause, cardiovascular or cancer mortality when compared to the women on the placebo arm when followed up for 18 years.[99] (Level I)

Women between 50 -59 years on the CEE and MPA combination showed a non-significant lowered mortality trend towards CVD, cancer and other causes

whilst those on CEE alone showed a significant age-related lowered mortality trend towards CVD, cancer and other causes.[99] (Level I)

The use of MHT in healthy young menopausal women is safe. MHT use should be individualized, taking into account

- The woman's personal health risks and preferences.
- Her signs and symptoms and its effect on her quality of life.
- Her age and/or time since menopause in relation to initiation or continuation of MHT.
- The balance of potential benefits and risks of MHT versus non-hormonal therapies or other options.[100] (Level I)

1.	Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms, genitourinary syndrome of menopause, prevention of bone loss and reduction of fractures.[97] (Level I)
2.	Benefits of menopausal hormone therapy (MHT) outweigh risks when given to healthy symptomatic women less than 60 years or within 10 years of menopause.[97] (Level I)
3.	Menopausal hormone therapy (MHT) treatment in women should always be individualized.[100] (Level I)

Recommendation 3

Women with menopausal symptoms who are less than 60 years of age or within 10 years of menopause should be offered menopausal hormone therapy for relief of vasomotor symptoms, genitourinary symptoms of the menopause and prevention of bone loss.[97] (Level I)

5.2 Starting Menopausal Hormone Therapy

Prior to starting MHT, a detailed history, examination and counselling is mandatory. The risks and benefits of MHT to the potential user is discussed and a well-informed decision is then made. *(Appendix 5)*

MHT is approved for four indications[97, 101 (Level I)]

- **Vasomotor symptoms (VMS):** MHT reduces hot flushes and night sweats and is recommended as first line-therapy for women with moderate to severe VMS.[102 (Level I)]

- **Prevention of bone loss:** MHT prevents bone loss and reduces fractures in menopausal women. MHT decreases the incidence of all fractures, including vertebral and hip fractures, even in women not at high risk of fracture. MHT is the only therapy available with proven efficacy of fracture reduction in patients with osteopenia.[103,104 (Level I)]

- **Hypoestrogenism:** For women with hypoestrogenism caused by hypogonadism, POI, or premature surgical menopause, hormonal therapy either as the low dose COC or MHT is recommended at least until the median age of menopause (50 years). Hormonal therapy relieves VMS, prevents bone loss, and improves cognition, mood disorders and improves lipid profiles. A benefit- risk assessment is carried out annually if MHT is continued beyond 50 years.[21 (Level II-3), 105, 106, 107, 108, 109 (Level I)]

- **Genitourinary syndrome of menopause (GSM):** In primary menopause-related GSM issues, low-dose vaginal ET is recommended over systemic ET as first-line hormonal therapy. MHT has been shown to effectively restore genitourinary tract anatomy, increase superficial vaginal cells, reduce vaginal pH, and treat symptoms of vulvovaginal atrophy (VVA).[110 (Level I)]

Contraindications to MHT include women with past or present history of the following conditions:[111 (Level I)]

- Breast or endometrial cancer (any hormone related cancer).
- Blood clots, particularly in the lungs, eyes, or deep veins.
- Heart attack, stroke, or transient ischemic attack (TIA).
- Liver disease or liver problems.
- Inadequately controlled arterial hypertension

- Undiagnosed uterine or vaginal bleeding.
- Porphyria.
- Pregnancy.

Menopausal hormone therapy is approved for use in women experiencing vasomotor symptoms, for prevention of bone loss and reduction of fractures, genitourinary syndrome of menopause and for women with hypoestrogenism due to hypogonadism and premature ovarian insufficiency. [97, 101 (Level I)]

5.3 Types of Menopausal Hormone Therapy

The estrogen and progestogen component of MHT can differ in type and dose, and are available in different combinations and delivery systems.

Hysterectomised women need estrogen therapy only (ET).[101 (Level I)]

Non-hysterectomised women (intact uterus) require both estrogen and progestogen (EPT). This can be given as a cyclical preparation (in peri-menopausal women and up to the first year of the last period) or as continuous combined preparation in postmenopausal women (one year after the last period).[101 (Level I)] *(Appendix 6)*

Cyclical therapy

Women in the perimenopause and up to one year from their last period are advised the cyclical therapy; estrogen is administered daily while progestogen is added for at least 12-14 days of the cycle to provide endometrial protection. Women would experience regular monthly bleeds.[112 (Level I).]

Continuous combined therapy

Women one year or more from their last period are advised the continuous combined therapy, also called the "no bleed therapy"; estrogen and progestogen is taken daily. Initial spotting or staining (break through bleeding) is common up to six months, after which there should not be any bleeding [112 (Level I)]

The use of continuous combined preparations in perimenopausal women is not encouraged due to the increased risk of irregular bleeding. Perimenopausal women who are further away from their last menstrual period have lesser break through bleeding than those closer to their last period.

Missing a pill or being non-compliant with the prescribed dosage may also cause irregular bleeding. Unscheduled bleeding beyond 6 months of use should always be investigated.[112 (Level I).]

Estrogen

The most commonly prescribed estrogen is estradiol valerate, estradiol hemihydrate, 17 beta estradiol and conjugated equine estrogen (CEE). Different types of estrogen have different effects on the brain, cardiovascular system, stroke and venous thromboembolism.[113,114 (Level II-3)] *Please see Section 5.9.*

Progestogens

The commonly found progestogens in local MHT preparations are dydrogesterone, mircronised progestogen, levonorgestrel, drospirenone, medroxyprogesterone acetate (MPA) and norethindrone acetate.[115 (Level I)]

Different progestogens have different effects on the cardiovascular disease, venous thromboembolism and breast tissue.[114 (Level II-3)] *Please see Section 5.10*

Progestogen therapy is not required if only low-dose vaginal ET is used. However appropriate evaluation of the endometrium should be performed if abnormal vaginal bleeding occurs.[116 (Level I)]

Table 8 outlines the different estrogen and progestogen preparations in Malaysia.

Table 8: Different types and doses of estrogen and progestogen in the various MHT preparations in Malaysia.[117 (Level IV)]

Estrogen	Progestogen
Estradiol Hemihydrate 1 mg, 2 mg	Dydrogesterone 10 mg
Estradiol Valerate (EV) 1mg, 2 mg	Cyproterone Acetate 1 mg
Conjugated equine estrogen (CEE) 0.3 mg, 0.625 mg	Norgestrel 500 mcg
17 beta estradiol 1.25 gm, 2.5 gm	Drospirenone 2 mg
Estradiol gel 1mg, 2mg	Micronised progesterone 100 mg
Estradiol spray 1.53mg	Medroxy progesterone acetate 10 mg
	Levonorgestrel intrauterine system (LNG IUS)

1.	Hysterectomised women need only estrogen therapy (ET).[101 (Level I)]
2.	Women with an intact uterus need both estrogen and progestogen (EPT).[101 (Level I)]
3.	Symptomatic women (with intact uterus) in the perimenopause and up to one year of menopause are put on cyclical hormone therapy; which constitutes daily estrogen with progestogen for 12 – 14 days a month for endometrial protection; leading to regular scheduled periods.[112 (Level I).]
4.	Symptomatic women (with intact uterus) who are one year after menopause are advised the “no bleed therapy” or the continuous combined preparation; which constitutes daily estrogen and progestogen use.[112 (Level I)]
5.	Irregular bleeding after six months of continuous combined therapy should always be investigated.[112 (Level I).]

Recommendation 4	
1.	Hysterectomised women (women without a uterus), need only estrogen therapy for relief of menopausal symptoms.[101 (Level I)]
2.	Non-hysterectomised women (women with an intact uterus) need both estrogen and progestogen therapy for relief of menopausal symptoms. Progestogen is added for endometrial protection.[101 (Level I)] • Cyclical therapy (regular scheduled periods) is prescribed for women in the perimenopause.[112 (Level I)] • Continuous combined therapy (no bleed therapy) is prescribed for women who are one year from their last period.[112 (Level I)]
3.	Low dose vaginal estrogen therapy is advised for relief of symptoms of genitourinary syndrome of menopause; additional progestogen therapy is not needed for endometrial protection. However, any unscheduled vaginal bleeding should always be investigated.[116 (Level I)]

5.4 Delivery Routes

MHT may be delivered via oral, transdermal, vaginal and intrauterine routes. These delivery systems allow for individualisation of MHT treatment in women.

In Malaysia, estrogen replacement therapy is available either as an oral tablet, a transdermal gel or spray. In women with an intact uterus, progestogen is always added to estrogen for endometrial protection. The types of estrogen and progestogen available for use in MHT preparations in Malaysia is listed in *Table 9*.

Micronised progesterone can be used orally or vaginally. The levonorgestrel intrauterine system (LNG-IUS) is an ideal progestogen for endometrial protection and can be combined with oral or transdermal estrogen.

Low-dose vaginal estrogen is available as a cream or as a tablet (which is in combination with probiotics) and is suited for women with GSM. The addition of progestogen is not required with vaginal estrogen therapy. Vaginal estrogen therapy is not indicated for the treatment of hot flushes, prevention of osteoporosis, heart disease, or other major health conditions.[101 (Level I)]

Women with estrogen-receptor positive breast cancer (past or present) can use vaginal estrogen therapy for GSM with no increased risk of breast cancer recurrence.[116] (Level II-1)

Non-oral routes of administration offer potential advantages on the clotting profile because it bypasses the liver (first-pass hepatic effect). No increased risk of stroke or VTE has been shown with transdermal estrogen preparations.[114] (Level II-3), 118 (Level II-1)

1.	Menopausal hormone therapy is available in the form of oral tablets, the transdermal gel or spray, vaginal progesterone tablets and the progestogen intrauterine system.[117] (Level III)
2.	Vaginal estrogen is primarily used for symptoms of genitourinary syndrome of menopause and is not indicated for the treatment of hot flushes, prevention of osteoporosis, heart disease, or other major health conditions.[101] (Level I)
3.	Non-oral routes of administration offer potential advantages on the clotting profile because it bypasses the liver (first-pass hepatic effect). No increased risk of stroke or venous thromboembolism has been shown with transdermal estrogen preparations.[114] (Level II-3), 118 (Level II-1)

Recommendation 5	
1.	Women with menopausal symptoms who are at a higher risk of stroke or venous thromboembolism are advised to use transdermal estrogen preparations for relief of menopausal symptoms. Women with an intact uterus will still need to add 12 -14 days of either oral or vaginal progestogen or use the levonorgestrel intrauterine system (LNG-IUS) for endometrial protection.[114] (Level II-3), 118 (Level II-1)
2.	Women with estrogen-receptor positive breast cancer (past or present) are advised vaginal estrogen therapy for symptoms of genitourinary syndrome of menopause. There is no increased risk of breast cancer recurrence.[116] (Level II-1)

5.5 Available Menopausal Hormone Therapy in Malaysia

The various preparations of MHT available in Malaysia is listed below.

Table 9: Menopausal Hormone Therapy preparations available in Malaysia[117] (Level III)

Estrogen only Preparations **Oral Route**

NAME	CONTENTS	TYPE	USAGE
PREMARIN TABLETS 0.3 mg	Conjugated equine estrogen (CEE). Low dose	Low dose Estrogen only tablets	28 tablets in each pack. Estrogen only tablets for hysterectomised women. One tab daily. May be used in combination with progestogen for cyclical or continuous combined therapy.
PREMARIN TABLETS 0.625 mg	Conjugated equine estrogen (CEE).	Estrogen only tablets	
PROGYNOVA 1 mg	Estradiol valerate Low dose.	Low dose Estrogen only tablets.	
PROGYNOVA 2 mg	Estradiol valerate.	Estrogen only tablets	

Estrogen only Preparations **Transdermal Route**

NAME	CONTENTS	TYPE	USAGE
OESTROGEL	17beta-estradiol. 1/2 ruler = 1.25 gm of 17beta-estradiol. (low dose) 1 ruler = 2.5 gm of 17beta-estradiol.	Transdermal estrogen cream.	Estrogen only for hysterectomised women. May also be used in combination with progestogen for cyclical or continuous combined therapy.

NAME	CONTENTS	TYPE	USAGE
DIVIGEL 1 mg	Estradiol gel (low dose) 1 sachet	Transdermal estrogen cream	28 sachets in each box Estrogen only for hysterectomised women. 1 or 2 (as adviced) sachet (s) to be applied daily to upper arm or thigh. May be used in combination with progestogen for cyclical or continuous combined therapy.
LENZETTO 1.53 mg	Estradiol spray	Transdermal estrogen spray	Estrogen only for hysterectomised women. 2 sprays daily on the forearm. The dose may be increased to 3 sprays daily if required. May be used in combination with progestogen for cyclical or continuous combined therapy

Estrogen only Preparations

Transvaginal Route for Genitourinary Syndrome of Menopause

NAME	CONTENTS	TYPE	USAGE
PREMARIN VAGINAL CREAM	Conjugated equine estrogen (CEE) 42.5gm/tube	Vaginal estrogen cream	For moderate to severe dyspareunia due to menopause: 0.5 gm of vaginal cream twice a week until as directed. Not to be used as a vaginal lubricant.

Cyclical Estrogen / Progestogen Preparations

NAME	CONTENTS	TYPE	USAGE
FEMOSTON 1/10	14 orange tablets each containing estradiol hemihydrate 1 mg 14 yellow tablets each containing estradiol hemihydrate 1 mg & dydrogesterone 10 mg	Cyclical MHT (with low dose estrogen)	Each box has 28 tablets. One tablet daily at the same time. No break between boxes. Regular scheduled bleeding.
FEMOSTON 2/10	14 white tablets each containing estradiol hemihydrate 2 mg 14 blue tablets each containing estradiol hemihydrate 2 mg & dydrogesterone 10 mg	Cyclical MHT	
CLIMEN 28	16 white tablets each containing estradiol valerate 2 mg 12 pink tablets each containing estradiol valerate 2 mg & cyproterone acetate 1 mg	Cyclical MHT	

NAME	CONTENTS	TYPE	USAGE
PROGYLUTON	11 white tablets each containing estradiol valerate 2 mg, 10 brown tablets each containing estradiol valerate 2 mg & norgestrel 500 mcg	Cyclical MHT	Each box has 21 tablets. One tablet daily at the same time. 7 day break between boxes. Regular scheduled bleeding

Continuous Combined Estrogen / Progestogen Preparations

NAME	CONTENTS	TYPE	USAGE
ANGELIQ	Each tablet contains estradiol 1 mg & drospirenone 0.5 mg	Continuous Combined MHT (with low dose estrogen and progestogen)	28 tablets in each box One tablet daily at the same time. No break between boxes. Initial spotting or staining for the first 6 months is accepted after which there is no bleeding. Unscheduled bleeding should be always be investigated.
FEMOSTON CONTI 1/5	Each orange tablet contains estradiol hemihydrate 1 mg & dydrogesterone 5 mg	Continuous Combined MHT (with low dose estrogen and progestogen)	

Progestogens

NAME	CONTENTS	TYPE	USAGE
UTEROGESTAN	100 mg micronised progesterone	100 mg (low dose) or 200 mg daily as prescribed	30 tablets in each box. Can be used orally or as vaginal inserts. Used in combination with estrogen (orally or transdermal) either cyclically or in a continuous combined preparation.
PROVERA	5 /10 mg of medroxyprogesterone acetate	5 mg (low dose) or 10 mg daily as prescribed	Used in combination with estrogen (orally or transdermal) either cyclically or in a continuous combined preparation.
DUPHASTON	10 mg of dydrogesterone	10 mg daily as prescribed	
MIRENA LNG-IUS	52 mg LNG (levonorgestrel) 20 mcg released daily	Intrauterine system lasting 5 years	

The above list is accurate up to the date of printing of this guideline.

5.6 Benefits and Risks of Menopausal Hormone Therapy

Risks of MHT differ with the type of estrogen or progestogen used, dose and duration of use, route of administration, timing of initiation, and whether only estrogen or an estrogen / progestogen combination is prescribed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic re-evaluation. There is presently no fixed duration for the use of MHT.

In healthy symptomatic women who are less than 60 years or within 10 years of menopause and with no contraindications to its use, the benefit-risk ratio of MHT use is favourable towards VMS, GSM and bone health.[116 (Level I)]

However, for maximum cardio protective efficacy, a woman should initiate MHT as soon as VMS symptoms occur, and preferably within the first 10 postmenopausal years. Hormone therapy is not indicated for primary or secondary cardio protection.[122 (Level I)]

For women who initiate MHT after the age of 60 years or 10 years after menopause, the benefit-risk ratio may be associated with greater absolute risks towards CHD, stroke, VTE, and dementia.[122 (Level I)]

Recent evidence suggests that the use of CEE and estradiol-based MHT regimes do not endanger the heart, but significantly reduces the incidence of atherosclerosis, CHD events and mortality.[122 (Level I), 123 (Level II-3)]

Younger women who go through surgical menopause are advised ET (in the absence of contraindications) to prevent immediate and long-term problems of the menopause especially to the bone, brain and heart.[124 (Level I)]

The benefits and risks of MHT on specific areas is detailed in Section 6 and Appendix 5.

1.	In women less than 60 years or within 10 years of menopause and with no contraindications to its use, the benefit-risk ratio of menopausal hormone therapy (MHT) treatment is favourable towards relief of vasomotor symptoms, symptoms of genitourinary syndrome of menopause and bone health. [116 (Level I)]
2.	Women who initiate menopausal hormone therapy 10 years after menopause have a higher absolute risk of coronary heart disease, stroke, venous thromboembolism and dementia. [122 (Level I)]

Recommendation 6	
1.	Women with menopausal symptoms who are less than 60 years of age or within 10 years of menopause, should be offered menopausal hormone therapy for treatment of vasomotor symptoms, symptoms of genitourinary syndrome of menopause and for bone health.[116 (Level I)]
2.	For maximal cardio protective efficacy, women should start menopausal hormone therapy with the onset of vasomotor symptoms and within 10 years of menopause.[122 (Level I)]
3.	Younger women who undergo surgical menopause are advised to take ET till the age of 50 years to prevent immediate and long-term problems of the menopause.[124 (Level I)]

5.7 Duration of Use of Menopausal Hormone Therapy

There is presently no mandatory limitation to duration of MHT use. Post-menopausal women can continue MHT as long as an annual review which includes a benefit – risk assessment and relevant investigations are carried out. Low dose MHT along with the most appropriate route of administration should be used if long term MHT is considered.[88 (Level II-1), 101 (Level I)] *(see Section 5.11)*

The factors to be taken into consideration for continuous use of MHT include:

- the patient's personal preferences.
- yearly review with benefit- risk assessment.
- whether the primary use of MHT is for prevention or for QOL purposes. [8(Level II-3)]

Continued use of MHT (beyond 10 years) will benefit women with persistent VMS symptoms, improve GSM symptoms, increase bone density and reduce fractures at all sites.[8(Level II-3)]

In women with POI or early menopause (natural, induced, surgical), early initiation of either low dose COC or MHT till the natural age of menopause (50 years) is recommended. MHT may be continued after the age of 50 years if the benefits of continued use of hormones outweighs the risks.[101 (Level I)]

With discontinuation of MHT:

- VMS has an approximately 50% chance of recurring. This is independent of the woman's age and her duration of MHT use.[124, 125 (Level II-1)]
- Further bone loss with increased risk of fractures may occur.[126 (Level I), 127 (Level II-3)]
- Symptoms of GSM may recur.[128 (Level I)]

1.	There is presently no mandatory limitation to duration of menopausal hormone therapy use.[88 (Level II-1), 101 (Level I)]
2.	Post-menopausal women can continue menopausal hormone therapy as long as an annual review which includes a benefit – risk assessment and relevant investigations are carried out.[128 (Level I)]
3	Continued use of menopausal hormone therapy (beyond 10 years) will benefit post-menopausal women with persistent vasomotor symptoms, improve symptoms related to genitourinary syndrome of menopause, increase bone density and reduce fractures at all sites.[88 (Level II-1), 101 (Level I)]
4.	Stopping menopausal hormone therapy may cause a recurrence in vasomotor symptoms,[124, 125 (Level II-1)] symptoms related to genitourinary syndrome of menopause[128 (Level I)] and further bone loss with an increased risk of fractures.[126 (Level I), 127 (Level II-3).]

Recommendation 7	
1.	Post-menopausal women are allowed to continue menopausal hormone therapy without any mandatory time limit as long as an annual review with relevant investigations (see Section 5.11) and an annual benefit-risk assessment is carried out.[128 (Level I)]
2.	When long term menopausal hormone therapy (beyond 10 years) is considered, a low dose hormonal regime is advised.[88 (Level II-1), 101 (Level I)]
3.	Continued use of menopausal hormone therapy (beyond 10 years) is recommended in post-menopausal women with persistent vasomotor symptoms, to improve symptoms related to genitourinary syndrome of menopause, to increase bone density and to reduce fractures at all sites.[8(Level II-3)]

5.8 Side Effects to Menopausal Hormone Therapy

Side effects with MHT are usually transient and may resolve spontaneously with continued use. Women are encouraged to persist with a particular hormone(s) for at least 3 months before switching or stopping so as to allow the initial side effects to settle. Side-effects are more likely to occur or be problematic when women are further into their menopause or further away from their last period.[88 (Level II-1)]

The side effects are usually related to the type of hormone used.

- Estrogen-related. As estrogen is administered daily these side effects occur continuously or randomly through the cycle.
- Progestogen-related. Progestogen related side effects are more problematic and are usually connected to the type, duration and dose of progestogen.[129 (Level II-1)] With cyclical therapy, the side effects appear during the progestogenic phase of the cycle. Those on the continuous combined preparations can have random side effects throughout the cycle.

Side effects to estrogen and progestogen are listed in *Table 10.*

Table 10: Possible side effects of estrogen and progestogen preparations[130 (Level III)]

Estrogenic Side effects	Progestogenic side effects
Breast tenderness	Breakthrough bleeding (BTB)
Leg cramps	Abdominal bloating
Nausea	Water retention
Dyspepsia	Migraine
Headaches	Breast tenderness
Abdominal bloating	Mood swings and depression
Indigestion	Premenstrual symptoms (PMS) symptoms
Vaginal bleeding	Acne
Water retention	Lower abdomen and back pain

Managing side effects of MHT

Breast Pain: MHT may initially cause breast pain due to the stimulation of breast glands. This discomfort will gradually settle in four to six weeks. The MHT dose can be lowered and with time increased to the normal dose. Alternatively, a change of progestogen or a complete switch to Tibolone may help.[131] (Level I)

Irregular bleeding: Women with an intact uterus need both estrogen and progestogen. Adequate progestogen for at least 12 -14 days of each cycle is added for endometrial protection.

Monthly cyclical preparations should produce regular, predictable and acceptable bleeding pattern starting towards the end or soon after the progestogen phase. This pattern may be altered by:[132](Level I)

- Irregular pill intake (non-compliance)
- Gastrointestinal upsets

Continuous combined preparations may cause breakthrough bleeding (BTB) up to six months of start of therapy. This occurs due to endometrial atrophy as the progestogen prevents normal cell regeneration.[132] (Level I)

Prolonged BTB beyond six months of MHT use (despite good compliance) must always be investigated to rule out pelvic pathology.[132] (Level I)

Abdominal bloating: Progestogen inhibits smooth muscle peristalsis of the gut resulting in bloating and abdominal distention. Bloating usually settles with time.[132] (Level I)

Weight gain: Weight gain may happen in the menopause due to lowered estrogen levels, loss of muscle tissue and lifestyle changes such as diet and lack of exercise. The increased weight tends to be stored more in the abdominal area which in turn increases the risk of metabolic problems.

Estrogen in MHT has been shown to redistribute the weight away from the abdominal area. Studies have shown that eighty percent of women on MHT do not change their weight over a period of 12 months. Up to 10% of women do gain weight, while another 10% of women lose weight while using MHT.[133] (Level I)

Appropriate dietary and lifestyle measures is always advised during menopause and with MHT use.

Leg cramps: Though not common, leg cramps do happen. Exercises and calf stretching movements help reduce the incidence of leg cramps.[134 (Level II-1)]

Nausea and dyspepsia: Altering the time of intake of oral MHT or a change to transdermal estrogen may help reduce gastrointestinal side effects. When taken or used at night, nausea may not be experienced. Oral MHT may also be taken with food to reduce gastric issues.[88 (Level II-1)]

Headaches: In women with persistent headaches, bypassing the liver with transdermal MHT may be considered. Transdermal estrogen produces a more stable estradiol level which may cut down the frequency of headaches.[135 (Level I)]

Mood swings and depression: Women on the combined MHT may exhibit mild mood changes which usually disappear with prolonged use.[136 (Level I)]

Side effects to menopausal hormone therapy are usually transient and resolves with time.[88 (Level II-1)]

Recommendation 8

Women on menopausal hormone therapy are encouraged to persist with the prescribed hormonal preparation for at least 3 months to allow the initial side effects to settle.[88 (Level II-1)]

5.8 (i) Management of Breakthrough Bleeding (BTB)

Breakthrough bleeding (BTB) is common in the first six months of a continuous combined MHT regime and does not need further investigations. Women who are not compliant with their prescribed hormone therapy may also experience BTB. However, persistent bleed or a new onset bleed needs further investigation by using the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified).[15 (Level III)]

Table 11 lists the different ways to handle break through bleeding.[130 (Level III)]

Table 11: Management of Breakthrough Bleeding (BTB)

Types of Break Through Bleeding	Management
Increased or prolonged bleeding	Increase progestogen dose. Increase duration of progestogen use from 14 days to 21 days. Change the type of progestogen. 120 (Level I)
Bleeding early in the progestogen phase	Increase the dose of progestogen. Change the type of progestogen. 130 (Level III)
Irregular bleeding on the continuous combined regime (once other causes are ruled out)	To switch to the cyclical regime for 3 months; then restart the continuous combined regime. 130 (Level III)

5.8 (ii) Cyclical therapy with absent scheduled bleeding

Five percent of women who are compliant on the cyclical therapy may not experience any bleeding due to presence of an atrophic endometrium. However, pregnancy must be ruled out.[137(Level I)]

1.	Breakthrough bleeding may be expected up to 6 months with a continuous combined preparation. Bleeding after 6 months of use should always be investigated based on the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified).[132 (Level I)]
2.	Amenorrhoea or no periods may occur in 5% of women on cyclical menopausal hormone therapy due to an atrophic endometrium; however, pregnancy should always be ruled out.[137(Level I)]

Recommendation 9	
1.	Women on menopausal hormone therapy who experience breakthrough bleeding after six months of continuous combined therapy should be investigated for pelvic pathology by using the FIGO classification system of PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory disorders, endometrial causes, iatrogenic causes and not otherwise classified). [132 (Level I)]
2.	Irregular bleeding while on menopausal hormone therapy can be managed by altering the dose, duration or type of progestogen.[120 (Level I), 130 (Level III)]

5.9 Choice of Estrogen in Menopausal Hormone Therapy

Estrogen preparations available in Malaysia are 17 beta estradiol, estradiol valerate, estradiol hemihydrate and conjugated equine estrogen (CEE). Different estrogen have different effects, especially on the brain serotonergic system, with estradiol providing a more robust anxiolytic and antidepressant effect.[113 (Level II)]

Both CEE and estradiol-based MHT regimes are safe for the cardiovascular system and significantly reduce the incidence of atherosclerosis, CHD events and mortality.[122 (Level I), 123 (Level II-3)]

17 beta estradiol is structurally similar to the major estrogen, estradiol (E2) that is secreted by the female ovary. Recent data has shown that estradiol carries a lower risk of VTE when compared to CEE and may be offered to women with a higher risk of CHD events and VTE.[114 (Level II-3)]

Transdermal estrogen is as effective as oral estrogen in alleviating vasomotor symptoms. It is also preferred over oral estrogen in women who are obese, women with hypertriglyceridemia, active gall bladder disease and known thrombophilia such as factor V Leiden. Transdermal estrogen preparations have been shown to decrease the risk of VTE.[114 (Level II-3), 118 (Level II-1)]

1.	17 beta estradiol is associated with a lesser risk of venous thromboembolism when compared to conjugated equine estrogen. [114 (Level II-3)]
2.	Transdermal estrogen is preferred over oral estrogen in women who are obese, women with hypertriglyceridemia, active gall bladder disease, and known thrombophilia such as factor V Leiden.[114 (Level II-3), 118 (Level II-1)]

Recommendation 10

Women with coexisting morbidities such as obesity, hypertriglyceridemia, active gall bladder disease, known thrombophilia such as Factor V Leiden and have a higher risk of venous thromboembolism; transdermal estrogen is preferred over oral estrogen preparations in these women as it is as effective for vasomotor symptoms with a lower risk of venous thromboembolism.[114 (Level II-3), 118 (Level II-1)]

5.10 Choice of Progestogen in Menopausal Hormone Therapy

Progestogens are substances that mimic the activity of endogenous progesterone present in the luteal phase of the menstrual cycle. The progestogens commonly used in Malaysia include dydrogesterone, micronised progesterone, levonorgestrel, drospirenone, micronized progesterone, medroxyprogesterone acetate (MPA) and norethindrone acetate.[115 (Level I)]

Their biological activity is varied, depending on the chemical structure, pharmacokinetics, receptor affinity and potency of action. The choice of progestogen depends on knowledge of its benefits, with a focus on minimizing potential side effects.[137, 138 (Level I)]

The menopausal hormone therapy combination of CEE and medroxyprogesterone (MPA) confer the highest risk for VTE (RR 2.10, 95% CI, 1.92 - 2.31) when compared to the estradiol / dydrogesterone preparation (RR 1.18, 95% CI, 0.98 -1.42).[114 (Level II-3)]

Progestogens such as micronised progesterone and dydrogesterone has not been shown to affect the cardiovascular system, or increase the risk of VTE and has minimal effect on the breast. The use of the LNG-IUS takes away the need of oral progestogens thus decreasing further risks to these areas *(see Table 12)*[137, 138 (Level I)].

Table 12: Progestogens in Menopausal Hormone Therapy[137, 138 (Level I)]

Type of Progestogen	Effects
Micronised Progesterone	A natural, 'body-identical' progesterone, devoid of any androgenic and glucocorticoid activity. It does not affect the cardiovascular system, blood pressure or increase the risk of venous thromboembolism (VTE) and stroke. Its anti-mineralocorticoid activity can cause slight hypotension. Observational studies have shown a lowered breast cancer risk.[137,138 (Level I)] It can be prescribed alongside oral or transdermal estrogen at a dose of 200

Type of Progestogen	Effects
	mgs per day for at least two weeks of a sequential therapy cycle. For women on a low dose continuous combined preparation, 100 mgs daily is recommended. If taken at night, it may aid sleep.
Dydrogesterone	Dydrogesterone is devoid of androgenic and glucocorticoid activity. It does not increase endometrial hyperproliferation, maintains the beneficial effects of estradiol and minimises progestogen associated risks to the cardiovascular system including stroke, VTE and to the breast tissue. it has minimal side effects.[37, 38 (Level I)]
LNG-IUS	The intrauterine levonorgestrel system is used as a contraceptive and for endometrial protection. The progestogen release is in utero which in turn leads to lesser systemic side effects. Estrogen may be added orally or as a transdermal preparation.[137, 138 (Level I)]
Drospirenone	This progestogen has anti androgenic properties along with anti-mineralocorticoid activity. It may help women with slightly elevated blood pressure.

1.	Micronised progesterone does not affect the blood pressure or the cardiovascular system, does not increase the risk of venous thromboembolism (VTE) and stroke and has minimal effect on the breast.[137, 138 (Level I)]
2.	Dydrogesterone does not increase endometrial hyper proliferation, maintains the beneficial effects of estradiol (i.e., efficacy against menopausal symptoms and prevention of osteoporotic fractures) and minimizes progestogen associated risks to the breast and cardiovascular system (stroke and venous thromboembolism).[137, 138 (Level I)]
3.	The intrauterine levonorgestrel system (LNG-IUS) is used as a contraceptive and for endometrial protection. Estrogen for menopausal hormone therapy may be added orally or through the transdermal route.[137, 138 (Level I)]

Recommendation 11	
1.	Women with menopausal symptoms who need combined estrogen-progestogen therapy are advised progestogens such as micronised progesterone or dydrogesterone as recent data has shown it to be safer on the cardiovascular system, risk of stroke and venous thromboembolism and has minimal effect on the breast.[137, 138 (Level I)]
2.	The levonorgestrel intrauterine system (LNG-IUS) is a good option for women with an intact uterus needing menopausal hormone therapy. It works both as a contraceptive and for endometrial protection. Estrogen therapy may be administered either orally or through the transdermal route.[137, 138 (Level I)]

5.11 Follow-Up of Women on Menopausal Hormone Therapy

Women who have initiated MHT should have an initial review after 3 months to check on side effects and effectiveness of treatment. Upon a satisfactory review, annual consultation is advised *(see Table 13)*. Clinical indications for an earlier review is given in *Table 14.*[88 (Level II-1)]

The annual consultation should include a physical examination, pelvic and breast examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle changes and strategies to prevent or reduce chronic disease. Annual benefit- risk assessments on the continued use of MHT should be carried out. Regular mammographic and cervical cancer screening should continue *(see Table 13)*.

A three-month trial of MHT is suggested to achieve maximum effect. During this time, improvement of symptoms should be noted and presence of residual symptoms should be discussed.

Table 13: During the follow up visit of patients on MHT

1. Blood pressure, pulse rate and BMI measurement.
2. Presence of side-effects such as breast tenderness, nausea, headaches and bleeding. Patients can be managed as in Section 5.8.
3. Presence of any new gynecological or non-gynecological problems.
4. Regular breast evaluation. Mammogram and / or breast ultrasound examinations are carried out 1-2 yearly depending on the results of the screening test and the individual's inherent risk of breast cancer.
5. Cervical screening to be done (if applicable) at 1-3 yearly intervals.
6. A review and discussion on the individual's benefit-risk ratio with MHT.
7. Relevant blood investigations, especially pertaining to lipids and glucose if necessary.

Table 14: Reasons for earlier follow up of patients on MHT[88 (Level II-1)]

1. Unscheduled vaginal bleeding
2. Persistent side effects to MHT
3. Persistent menopausal symptoms
4. Recent blood-clotting disorder
5. Recent symptoms of cardiovascular disease
6. Recent hormone-dependent breast cancer or another hormone-dependent cancer
7. Any recent new gynecological or non- gynecological problem that is of concern to the individual

Table 15: Factors to be considered if a patient remains symptomatic whilst on MHT

1. Gastrointestinal disturbances leading to poor absorption of MHT
2. Drug interactions which may reduce the bioavailability of estrogen e.g. carbamazepine, phenytoin
3. Other overriding medical problems which may mimic menopause e.g. hypothyroidism, diabetes
4. Inadequate estrogen dose
5. Patients' expectations that all menopausal symptoms will be resolved

There is no set duration for the use of MHT. Periodic assessments are emphasized and the decision to continue MHT should be based on the individual's symptoms and benefit-risk evaluation rather than being dependant on a specific time frame.[88 (Level II-1)]

If long term MHT is being considered, the most appropriate dose and route of administration should be used. Low dose MHT therapy is encouraged.[88 (Level II-1)]

Cessation of MHT can lead to recurring symptoms, especially VMS in up to 50% of women, which may impair quality of life.[88 (Level II-1)]

Women on menopausal hormone therapy should have a regular follow up; an initial three-month review is advised followed by annual review.
[88 (Level II-1)]

Recommendation 12	
1.	Women on menopausal hormone therapy are advised an initial 3 month follow up after commencement of hormones for review of side effects and alleviation of symptoms; followed by an annual benefit – risk assessment.[88 (Level II-1)]
2.	An earlier follow up is advised in case of serious side effects or if symptoms do not improve.[88 (Level II-1)] (Section 5.8 / Algorithm E)

5.12 Stopping Menopausal Hormone Therapy

There is presently no time limitation on the duration of MHT use. Women can continue MHT if they are followed up regularly, carry out scheduled investigations and their benefit-risk assessment is carried out annually.[101 (Level I)]

Women should be given correct information about the benefits and the potential risks of MHT. The fear of cancer and cardiovascular disease has caused many women who need MHT to abruptly stop MHT (against medical advice). *(see Appendix 5)*

The table below may help the health care provider and the MHT user make the appropriate decision to either stop or continue MHT.

Table 16. Reasons for stopping / continuing MHT

Stopping MHT	Continuing MHT
New contraindications	Absence of contraindications
More risks than benefits	More benefits than risks
Side effects	No side effects
Persistence of symptoms	Absence of symptoms
Patient's preference	Patient's preference

Women who stop MHT should be advised that menopausal symptoms may recur.

- Vasomotor symptoms (hot flushes and night sweats) usually last between two to five years. However, in some women, these symptoms may persist longer. If the rebound vasomotor symptoms are severe after stopping MHT, restarting treatment may be the most appropriate course of action.[88] (Level II-1)
- GSM symptoms may recur once MHT is stopped, resulting in a decline in pelvic and sexual health.[20] (Level I)
- Women who discontinue MHT, will lose BMD which can then increase the risk of osteoporosis and fractures.[126] (Level II-3)

It is vital for women with POI to continue using hormones (either low dose COC or MHT) as advised till the natural age of menopause (i.e., 50 years). Hormones are a necessity in these women especially for cardiovascular and bone protection. Unfortunately, up to 79% of women with POI prematurely stop hormonal therapy hormonal therapy due to unwarranted fears of breast cancer. Subsequent long-term effects with this cessation remain unclear.[139] (Level I)

Abrupt cessation or gradual withdrawal of HRT

There is no ideal way to stop MHT. Gradually decreasing the dose of MHT over three to six months is recommended, to minimize the rebound symptoms. However, studies have shown that the effect of stopping MHT abruptly may be similar to when it is tapered off slowly.[140] (Level II-3)

A woman is said to have successfully stopped her MHT if she has had none or only minimal symptoms after 2-3 months of MHT cessation.[141] (Level III-3)

In cases of severe rebound of symptoms, it is advised to continue low dose MHT for a longer period of time (preferably 3-6 months) prior to trying again.[141 (Level III-3)]

1.	Women who stop menopausal hormone therapy should be counselled about a possible recurrence in vasomotor symptoms, [88 (Level II-1)] worsening of symptoms related to genitourinary syndrome of menopause,[20 (Level I)] and loss of bone mineral density with an increased risk of fractures.[126 (Level II-3)]
2.	A woman is said to have successfully stopped her menopausal hormone therapy, if she has had none or only minimal symptoms after 2-3 months of hormone cessation.[141 (Level III-3)]

Recommendation 13	
1.	Menopausal hormone therapy should be ceased gradually over a period of 3-6 months rather than abruptly, to avoid a rebound of symptoms.[140 (Level II-3)]
2.	In case of severe rebound of symptoms, restarting low dose menopausal hormone therapy may be the most appropriate course of action prior to attempting again.[141 (Level III-3)]

Section 6: Effects of Menopausal Hormone Therapy

6.1 Menopausal Hormone Therapy in Perimenopause

The range of symptoms exhibited by the perimenopausal woman can vary widely *(see Table 1)*. Estrogen is the most effective treatment for perimenopausal related symptoms of hot flushes and night sweats, mood swings, anxiety, depression, disturbed sleep pattern and myalgia.[102 (Level I), 125 (Level II-1)]

Bleeding irregularities are also common during this transition. Contraception is important as the risk of pregnancy is 2-3% between ages of 45 to 50 years and 1% after the age of 50 years if still not menopaused.[141 (Level II-3)]

Non-hormonal medical treatments such as non-steroidal anti-inflammatory drugs and anti-fibrinolytic agents are first line therapy that is often used for heavy menstrual bleeding in the perimenopause.[14 (Level I)]

The low dose OCP or MHT is the ideal treatment for perimenopausal symptoms. The low dose OCP (in women without contraindications) can be used up to the age of 50 years. It is adequate as a contraceptive, achieves good cycle control and reduces perimenopausal symptoms. At 50 years, the low dose OCP is changed to MHT, if hormone therapy is still required.

Treatment with MHT alleviates perimenopausal symptoms and achieves good cycle control. However, it is inadequate as a contraceptive as the dose of estrogen and progestogen is less than that in the low dose OCP. Women above 50 years who are yet to reach menopause should be counselled about the 1% risk of pregnancy and additional contraceptive measures are to be taken.[15 (Level I)]

LNG-IUS reduces heavy menstrual bleeding in the perimenopause, works as a contraceptive, and can be used for endometrial protection. Women needing estrogen for perimenopausal symptoms can use oral or transdermal preparations.[16 (Level I)]

Counselling, management and follow up of a woman on hormonal therapy in the perimenopause would continue as in Section 3 and Section 5.

1.	Estrogen is the most effective treatment for perimenopausal symptoms such as hot flushes and night sweats, mood swings, anxiety, depression, disturbed sleep pattern and myalgia.[102 (Level I), 125 (Level II-1)]
2.	The low dose oral contraceptive pill is adequate as a contraceptive, achieves good cycle control and reduces perimenopausal symptoms.[14 (Level I)]
3.	Menopausal hormone therapy helps cycle control and alleviation of vasomotor symptoms in the perimenopause but is inadequate as a contraceptive.[15 (Level I)]
4.	The levonorgestrel intrauterine system can be used to control bleeding irregularities and for contraception in the perimenopause.[16 (Level I)]

Recommendation 14	
1.	Women with perimenopausal symptoms are advised either the • low dose oral contraceptive pill as it acts as a contraceptive, gives better cycle control and treats perimenopausal symptoms.[14 (Level I)] • menopausal hormone therapy which gives better cycle control and treats perimenopausal symptoms but is inadequate as a contraceptive. Non-hormonal contraception is advised, if necessary.[15 (Level I)]
2.	The levonorgestrel intrauterine system (LNG-IUS) is an alternative treatment for perimenopausal women with heavy menstrual bleeding. It acts as a contraceptive and provides endometrial protection. Women requiring menopausal hormone therapy can continue using the LNG-IUS and add estrogen either orally or via the transdermal route.[16 (Level I)]

6.2 Menopausal Hormone Therapy and Vasomotor Symptoms (VMS)

MHT is the first line therapy for relief of VMS and other associated symptoms such as disturbed sleep, irritability, concentration problems and diminished QoL.

The Cochrane data base looked at 24 blinded trials of menopausal hormone therapy against a placebo or a validated therapy, due to the large placebo effect seen even in well conducted randomised controlled trials, and also because menopause symptoms may fluctuate and often decline.[102 (Level I)] Standard doses of estrogen alone or in combination with progestogen has been shown to reduce the severity and frequency of VMS.[102 (Level I), 125 (Level II-1)] However low-dose MHT may take up to 6-8 weeks to control VMS symptoms.[143 (Level I)]

There is a 50% chance of recurrence of VMS when MHT is discontinued, independent of age of patient and duration of MHT use.[125 (Level II-1), 143 (Level II-3)]

Micronised progesterone (300 mgs) at night has been found to be effective in treating VMS, reducing hot flushes and improving sleep.[144 (Level I)]

1.	Menopausal hormone therapy is the first line therapy for relief of vasomotor symptoms and other associated symptoms such as disturbed sleep, irritability, concentration problems and diminished quality of life.[102 (Level I), 125 (Level II-1)]
2.	Lower doses of menopausal hormone therapy can take 6- 8 weeks to relieve vasomotor symptoms.[102 (Level I), 125 (Level II-1)]
3.	Micronised progestogens when taken at night have been found to be effective in treating vasomotor symptoms and improving sleep.[144 (Level I)]

Recommendation 15
Women should be offered menopausal hormone therapy for relief of vasomotor symptoms and other associated symptoms such as disturbed sleep, irritability, concentration problems and diminished quality of life which are related to the menopause.[102 (Level I), 125 (Level II-1)]

6.3 Menopausal Hormone Therapy and Mood Disorders

MHT is not an anti-depressant. Estrogen replacement may augment the effect of selective serotonin reuptake inhibitors (SSRIs) and have a positive effect on mood disorders.[145 (Level II)]

In the Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-Cog), 220 women were randomized to receive 4 years of 0.45 mgs per day oral conjugated equine estrogen plus 200 mgs per day micronised progesterone for the first 12 days of each month, 211 women were randomized to receive 50 ugs of transdermal estradiol daily plus 200 mgs per day of micronised progesterone for the first 12 days of each month, and 262 women were randomized to receive placebo pills and patches. Treatment with EPT significantly improved mood in the depression–dejection scale and tension-anxiety scale. Transdermal estrogen preparations did not show a similar benefit. These findings are limited to recently postmenopausal women with low cardiovascular risk profiles.[146 (Level I)]

Post-menopausal women with history of depression prior to menopause may experience a recurrence of depressive symptoms if MHT is withdrawn.[147 (Level I)]

1.	Estrogen does not act as an antidepressant but may augment the effect of selective serotonin reuptake inhibitors (SSRIs) and have a positive effect on mood disorders. [145 (Level II)]
2.	Oral estrogen has been shown to improve mood significantly; however transdermal estrogen preparations have not shown the same benefit.[146 (Level I)]
3.	Post-menopausal women with history of depression before menopause may experience recurrence of depressive symptoms if menopausal hormone therapy is withdrawn.[147 (Level I)]

Recommendation 16

Women experiencing menopause related mood changes are advised oral menopausal hormone therapy as it has a positive effect on mood disorders. Transdermal estrogen preparations may not show the same benefit.[146 (Level I)]

6.4 Menopausal Hormone Therapy and Genitourinary Syndrome of Menopause (GSM)

Estrogen therapy is the most effective treatment for GSM. Low-dose vaginal estrogen therapies which include creams, tablets and rings, are effective and safe with minimal systemic effects[101,110,148,149,150,151 (Level I)] The recent Cochrane review (2016) showed no difference in efficacy between different local estrogen preparations. Thirty RCTs were looked into and there was low-quality evidence that intra-vaginal estrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. However, there was no evidence of a difference in adverse events between the various estrogenic preparations compared with each other or with placebo.[110 (Level I)]

Topical vaginal estrogen used regularly for over two years has not been associated with endometrial hyperplasia. Concurrent use of progestogen for endometrial protection is not required.[150,153 (Level I)] The topical CEE cream when compared to oral CEE therapy significantly improved sexual function and dyspareunia in women with vaginal dryness.[154 (Level I)]

Ultra-low dose vaginal estriol 0.03mg in combination with Lactobacillus acidophilus KS400 for the treatment of postmenopausal vaginal atrophy has shown a significant improvement of the Vaginal Maturation Index (VMI) by 35.2% compared to 9.9% in placebo users over a period of three months. There was a further increase of VMI to 55.4% with longer use.[155 (Level I)]

Non-hormonal therapies that may improve GSM and is used for treatment of dyspareunia in post-menopausal women are as follows.

- Lubricants which mainly consist of a combination of protectants or thickening agents in a water-soluble base that have a maturation effect on the urogenital epithelium. Lubricants are primarily used to relieve vaginal dryness during intercourse and therefore do not provide a long-term solution.[153 (Level I)]

- Moisturizers are hydrophilic, insoluble, cross-linked polymers. They are usually used 2-3 times a week. Moisturizers help with vaginal dryness as they are bio-adhesive and retain water by attaching to mucin and epithelial cells on the vaginal wall.[153 (Level I)] A moisturizer containing a combination of hyaluronic acid 1% (for natural hydration of tissues) and l-arginine is available in Malaysia.

- Ospemifene (60mg/day) demonstrated a significantly greater Female Sexual Function Index (FSFI) score as compared to the placebo after four weeks of use. This effect persisted at 12 weeks and all domains of FSFI, which includes dyspareunia, arousal, and desire, were significantly improved.[156, 157,158, 159 (Level II-1)]

- The use of intravaginal 0.5% DHEA dehydroepiandrosterone (prasterone) for 12 weeks was associated with improvement in sex function (arousal / sensation domain, arousal / lubrication, orgasm and dryness).[160, 161 (Level II-1):162,163 (Level I)]

- Non-ablative laser therapy has been shown to improve vulvovaginal symptoms (vaginal dryness, burning, itching, dyspareunia, and dysuria) as well as Vaginal Health Index Score (VHIS) on a short-term basis. This form of therapy may need to be repeated at regular intervals.[164,167 (Level I); 165,166 (Level II-3)]

1.	Estrogen therapy is the most effective treatment for symptoms of genitourinary syndrome of menopause.[101,110,148,149,150,151 (Level 1)]

2.	Low-dose vaginal estrogen therapies (creams, tablets and rings) are effective and safe with minimal systemic effects.[101,110,148,149,150,151 (Level 1)]
3.	Topical vaginal estrogen used regularly over two years is not associated with endometrial hypertrophy.[150,153 (Level I)]
4.	Concurrent use of progestogens for endometrial protection is not required with vaginal estrogen therapy.[150,153 (Level I)]
5.	Non hormonal therapies such as lubricants, moisturisers, ospemifene and dehydroepiandrosterone may improve symptoms associated with genitourinary syndrome of menopause especially dyspareunia. 153,162,163 (Level I) 156, 157, 158, 159, 160, 161 (Level II-1)
6.	Non ablative laser therapy has been shown to improve vulvovaginal symptoms on a short-term basis but may need to be repeated at regular intervals.[164,167 (Level I); 165,166 (Level II-3)]

Recommendation 17
Women with symptoms related to genitourinary syndrome of the menopause are advised topical vaginal estrogen therapies as they are highly efficacious and carry minimal side effects.[101,110,148,149,150,151 (Level 1)]

6.5 Menopausal Hormone Therapy and Cardiovascular Disease and All-Cause Mortality

Menopausal hormone therapy is currently not recommended for primary or secondary prevention of coronary heart disease in women.

The effect of MHT on the heart is complex and is dependent on the age of the woman, her cardiovascular risk factors, whether only estrogen or an estrogen / progestogen combination is used, the type of estrogen or progestogen used along with the delivery methods of these hormones.

The potential beneficial effects of estrogen include:[168 (Level1)]

- An improvement in lipid profiles, primarily with oral estrogen.
- Enhanced endothelial function particularly in younger healthier women.

- Improved insulin sensitivity.

The potential adverse effects of estrogen are:[168 (Level1)]

- An increase in serum triglycerides with oral estrogen.
- Prothrombotic effects with oral estrogen.
- An increase in C reactive protein (CRP) through a non-inflammatory pathway.

Natural progesterone does not appear to negate the effects of estrogen on serum lipids.[168 (level1)] However, synthetic progestogens such as medroxyprogesterone acetate used in the WHI study and Estrogen / Progestin Replacement Study (HERS) may negate some of the good effects of estrogen on lipids and endothelial function.[98,169 (Level I)] Progestogens also increase CRP but through an inflammatory pathway.

Estrogen therapy when started within 10 years of menopause or for women less than 60 years of age may be cardio protective as compared with older postmenopausal women. This period is often referred to as the "estrogen window", "window of opportunity" or "timing hypothesis".[170,171 (Level I), 172 (Level III)]

In the Danish Osteoporosis Prevention Study (DOPS), younger women (around 50 years) taking MHT for 10 years had a reduced risk of mortality, heart failure, or myocardial infarction, without an increased risk in stroke, VTE, or cancer.[173 (Level I)]

In the 13-year follow-up report of the WHI trial on both ET and EPT, the absolute risks of adverse events in younger women were much lower than in older women and the quality-of-life benefits were more likely to outweigh risks if MHT was started early.[174 (Level I)] Younger and low risk women on ET showed a more favourable outcome to CVD (though not statistically significant) whilst those on EPT had a more neutral effect on CVD *(see Table 17).*[175 (Level I)]

A recent cumulative follow up of 18 years of the WHI study and its patients who were either on ET or EPT showed that MHT (with CEE plus MPA) for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular or cancer mortality.[99 (Level I)]

Transdermal estrogen has a more favourable effect than oral estrogen on markers for cardiovascular risk, is less thrombogenic and is associated with a lower risk of VTE than estrogen.[176 (Level I)]

Table 17: Age Specific Risks for Cardiovascular Disease. The Estrogen Window. A combined analysis of two WHI trials.[175 (Level I)]

Coronary Heart Disease

Age	Hazard Ratio (HR) (95% CI)	Absolute Excess Risks / 10,000 person years
50 – 59 years	0.93 (0.65 - 1.33)	-2
60 – 69 years	0.98 (0.79 - 1.21)	-1
70 – 79 years	1.26 (1 - 1.59)	+19

Coronary Heart Disease

Years since menopause	Hazard Ratio (HR) (95% CI)	Absolute Excess Risks / 10,000 person years
< 10 years	0.76 (0.5 - 1.16)	-6
10 - 19 years	1.10 (0.84 - 1.45)	+4
> 20 years	1.28 (1.03 - 1.58)	+17

1.	Menopausal hormone therapy is currently not recommended for primary or secondary prevention of coronary heart disease in menopausal women.[168 (Level1)]
2.	The absolute excess risk of cardiovascular disease is higher when menopausal hormone therapy is started in women above the age of 60 years or who are more than 10 years from menopause.[175 (Level I)]
3.	Transdermal estrogen has a more favourable effect than oral estrogen on markers for cardiovascular risk, is less thrombogenic and is associated with a lower risk of venous thromboembolism than oral estrogen.[176 (Level I)]

Recommendation 18

Menopausal hormone therapy is the recommended treatment for post-menopausal symptoms in women less than 60 years of age and within 10 years of menopause as the risk of cardiovascular disease is lower in this age group when compared to older post-menopausal women.[175 (Level I)]

6.6 Menopausal Hormone Therapy and Stroke

Initiation of MHT in women under 60 years old and within 10 years of menopause has minimal effect on the risk of stroke.[98,177 (Level I)]

The absolute risk of stroke from standard dose oral hormone therapy is about 2 additional strokes per 10,000 person-years, equivalent to one additional stroke among 1000 women using hormone therapy for five years.[178 (Level I)]

Risk of ischaemic stroke is increased when MHT (either ET or EPT) is initiated in women more than 60 years old or more than 10 years after menopause.[179 (Level II-2)]

Table 18: Age specific risks for Stroke with MHT use[175 (Level I)]

Age	EPT Hazard Ratio (HR) (95% CI)	ET Hazard Ratio (HR) (95% CI)
50 – 59 years	1.41 (0.75 – 2.65)	0.89 (0.47 - 1.69)
60 – 69 years	1.37 (0.95 – 1.97)	1.63 (1.15 – 2.27)
70 – 79 years	1.21 (0.82 - 1.78)	1.20 (0.93 – 1.55)

Presence of cardiovascular risk factors (diabetes, hypertension, dyslipidaemia) have been shown to increase the risk of stroke when on oral MHT. Transdermal MHT preparations (estrogen alone or in combination with micronized progesterone or dydrogesterone) does not increase this risk.[20 (Level I)]

1.	Initiation of menopausal hormone therapy in women under 60 years old and within 10 years of menopause has minimal effect on the risk of stroke when compared to older post-menopausal women.[98,177 (Level I)]
2.	Risk of ischemic stroke is increased when menopausal hormone therapy (either estrogen therapy or estrogen-progestogen therapy) is initiated in women more than 60 years old or more than 10 years of menopause.[179 (Level II-2)]
3.	Presence of cardiovascular risk factors (diabetes, hypertension, dyslipidaemia) have been shown to increase the risk of stroke when on oral menopausal hormone therapy.[20 (Level I)]

Recommendation 19

Menopausal hormone therapy is the recommended treatment for post-menopausal symptoms in women less than 60 years of age and within 10 years of menopause as the risk of stroke is minimal in this age group when compared to older post-menopausal women.[98,177 (Level I), 179 (Level II-2)]

6.7 Menopausal Hormone Therapy and Venous Thromboembolism (VTE)

In relatively healthy, recently menopaused women, the risk of VTE is minimal.[118 (Level II-1),]

The risk of VTE increases slightly with oral MHT but the absolute risk is still rare below the age of 60 years. Oral ET is contraindicated in women with history of VTE.[20 (Level I)]

Table 19: Age specific risks for VTE with MHT use[175 (Level I)]

Age	Hazard Ratio (HR) for VTE (95% CI)
0 – 59 years	0.71 (0.40 – 1.26)
60 – 69 years	1.20 (0.82 – 1.76)
70 – 79 years	1.26 (0.79 – 1.99)

Estradiol is now seen as the preferred estrogen to be used either alone (in hysterectomised women) or in combination with micronised progesterone or dydrogesterone (in women with an intact uterus) as it carries a lower risk of VTE.[114 (Level II-3)]

Transdermal estrogen used alone or in combination with micronized progesterone is not associated with an increased risk of VTE as compared to oral ET or EPT.[114 (Level II-3),180 (Level III); 181,182 (Level I)]

Obesity is a significant risk factor to increase the risk of VTE in MHT users. Transdermal preparations of MHT has not shown to increase the risk of VTE in obese women.[181 (Level I)]

1.	The risk of venous thromboembolism increases slightly with oral menopausal hormone therapy but the absolute risk is still rare below the age of 60 years.[20 (Level I)]
2.	Transdermal estrogen alone or combined with micronised progesterone was not associated with an increased risk of venous thromboembolism as compared to oral estrogen therapy or estrogen-progestogen therapy.[114 (Level II-3),180 (Level III); 181,182 (Level I)]
3.	Obesity can increase the risk of venous thromboembolism in menopausal hormone therapy users. Transdermal preparations does not increase this risk.[181 (Level I)]

Recommendation 20

Menopausal hormone therapy is the recommended treatment for post-menopausal symptoms in women less than 60 years of age and within 10 years of menopause as the risk of venous thromboembolism is minimal in this age group when compared to older post-menopausal women.[20 (Level I)]

6.8 Menopausal Hormone Therapy and Osteoporosis

MHT is first-line treatment for the prevention and treatment of postmenopausal osteoporosis in women below 60 years.[183 (Level I)]

MHT consisting of either estrogen alone or in combination with progestogen slows bone turnover and increases BMD at all skeletal sites in early and late postmenopause.[183 (Level I)] MHT also decreases fragility fracture risk (spine, hip and non-vertebral sites) by 20-35%.[103,104 (Level I)]

Low dose MHT has been shown to protect bone by decreasing bone turnover markers (BTM) and preventing bone loss. However, their anti-fracture efficacy has not been confirmed.[184, 185 (Level II-1)]

The maximum bone protection is seen when estrogen therapy is given soon after menopause, and is maintained as long as MHT is continued. Discontinuation of MHT results in accelerated bone turnover, decrease in BMD and loss of anti-fracture efficacy.[186 (Level II-3), 187 (Level II-1)]

Use of MHT for prevention or treatment of osteoporosis in younger women (< 60 years of age) and those who are recently menopausal, has not been shown to increase the risk of cardiovascular events, stroke, venous thromboembolism (VTE) and haemorrhagic stroke.[97 (Level I)]

In women above 60 years or more than 10 years from the menopause, other non-hormonal bone-active therapy is required for osteoporosis and prevention of fragility fractures.[188 (Level I)]

1.	Menopausal hormone therapy is the first-line treatment for the prevention and treatment of postmenopausal osteoporosis in women below 60 years.[183 (Level I)]
2.	Menopausal hormone therapy slows bone turnover, increases bone mineral density at all skeletal sites and decreases fragility fractures in early and late post menopause.[103,104 (Level I)]
3.	Low dose menopausal hormone therapy decreases bone turnover markers however the data on fracture efficacy is unclear.[184, 185 (Level II-1)]
4.	Discontinuation of menopausal hormone therapy results in accelerated bone turnover, decrease in bone mineral density and loss of anti-fracture efficacy.[186 (Level II-3), 187 (Level II-1)]

Recommendation 21
Menopausal hormone therapy treatment recommended for the treatment of menopausal symptoms in women less than 60 years of age or within 10 years of menopause helps prevent and treat post-menopausal osteoporosis.[183] (Level I)

6.9 Menopausal Hormone Therapy and Sarcopenia

The skeletal frame is held up by muscles; preserving muscle strength and prevention of sarcopenia helps prevent physical disability. The role of estrogen, as a potential cause of sarcopenia remains controversial. The current consensus is that the physical and metabolic consequences of sarcopenia are neither specific to menopause nor gender.

The current gold standard in the management of sarcopenia emphasizes improved nutrition and resistance training as it has been shown to be effective in attenuating age-related muscle loss and strength.

A large systematic review and meta-analysis carried out in 2018 did not show a significant benefit of MHT on muscle mass.[189] (Level I)

1.	The role of estrogen as a potential cause of sarcopenia remains controversial.[189] (Level I)
2.	There are currently no recommendations for use of menopausal hormone therapy as a prevention or treatment strategy for sarcopenia in the menopause.[189] (Level I)

Recommendation 22
There are currently no recommendations for use of menopausal hormone therapy as a prevention or treatment strategy for sarcopenia in the menopause.[189] (Level I)

6.10 Menopausal Hormone Therapy and Metabolic Disease, Weight, and Diabetes

MHT has a beneficial effect on the metabolic system.

In women without diabetes, MHT causes the following changes:[190,191 (Level I)]

- An increase in lean body mass [3.3% (CI, 0.02–6.6%)].
- Reduction in waist circumference [0.8% (CI, 1.2 to 0.4%)].
- Reduction in abdominal fat [6.8% (CI, 11.8 to 1.9%)].
- Significant reduction in fasting glucose levels [2.5%, (CI, 1.5–3.5%)].
- Significant reduction in insulin levels [9.3%, (CI, 4.9–13.7%)].
- Significant reduction in insulin resistance, HOMA-IR [12.9%, (CI, 8.6–17.1%)].
- A 30%- 40% reduction in new onset diabetes [RR 0.7 (CI, 0.6–0.9)].

In women with diabetes, MHT has the following effects:[190,191 (Level I)]

- A reduction in "homeopathic model assessment of insulin resistance" (HOMA-IR) by 35.8% (CI, 19.8–51.7%) compared to placebo or no treatment. A greater reduction in HOMA-IR was seen in women with diabetes compared to those without known diabetes, (p = 0.007).
- A reduction of fasting glucose by 11.5% (CI, 5.1– 18.0%).
- A reduction of fasting insulin by 20.2% (CI, 4.2–36.3%).

The benefits and risks of MHT use must be taken into consideration when assessing the atherosclerotic risk in women. MHT has been shown to increase high density lipoprotein (HDL) cholesterol and reduce low density lipoprotein (LDL) cholesterol, lipoprotein a (Lp (a)), mean blood pressure, fibrinogen and plasminogen activator inhibitor-1 (PAI-1). However, oral estrogen has been shown to increase triglyceride levels.[190 (Level I)]

Timing of initiation of MHT appears to have differential effects on insulin action. There is an improvement in insulin stimulated glucose disposal when MHT is given to women who were <6 years postmenopausal, while a reduction in glucose disposal was found in women who were >10 years postmenopausal.[99 (Level Ib), 192 (Level I)]

Unfortunately, despite the favourable effects of MHT on the parameters of metabolic syndrome (MetS), insulin resistance and reduction in onset of T2DM, there are currently no recommendations for use of MHT as a prevention strategy for metabolic disorders in menopause.

1.	Menopausal hormone therapy has a beneficial effect on the metabolic system; however, it is not recommended as first line therapy for prevention of metabolic problems.[190,191 (Level I)]
2.	Menopausal hormone therapy is beneficial in post-menopausal women with or without diabetes. There is an increase in lean body mass, reduction in waist circumference, significant reduction in fasting glucose levels, insulin levels and insulin resistance and a 30%- 40% reduction in new onset diabetes.[190,191 (Level I)]
3.	There is an improvement in insulin stimulated glucose disposal when menopausal hormone therapy is given to women who were <6 years postmenopausal, while a reduction in glucose disposal was found in women who were >10 years postmenopausal.[99 (Level Ib), 192 (Level I)]

Recommendation 23
There are currently no recommendations for use of menopausal hormone therapy as a prevention or treatment strategy for metabolic disorders in the menopause.[190,191 (Level I)]

6.11 Menopausal Hormone Therapy and Cognition

Estrogen plays a role in cognition through its effect on the cholinergic and glutamate system and its ability to stimulate neurons and protect nerve cells. It has also been linked to prevention of amyloid in Alzheimer's Disease (AD).[193,194] (Level I)

Though some epidemiological and observational data of MHT in younger postmenopausal women has shown that estrogen protects against cognitive impairment in the later years, the WHI Memory Study [WHIMS),[195](Level I), 196 (Level II-1)], the Kronos Early Estrogen Prevention Study (KEEPS) trial[146 (Level I)] and the Early versus Late Intervention Trial with Estradiol (ELITE) trial showed no beneficial effects of estrogen therapy on cognition. However, the recent long term follows up from the WHI study have shown that there is a reduction in deaths from Alzheimer's' disease and other dementia in the ET users.[99 (Level I)]

MHT use in early menopausal women and within 10 years of menopause is safe. However, MHT should not be prescribed solely for cognition or for the reduction of AD.[195, 196 (Level II)]

1.	Estrogen plays a role in cognition by its effect on the cholinergic and glutamate system, by stimulating neurons, protecting nerve cells and is linked to prevention of amyloid in Alzheimer's Disease.[193,194 (Level I)]
2.	Most studies have not shown a beneficial effect of estrogen on the brain.[146, 195(Level I), 196 (Level II-1)]

Recommendation 24

Menopausal hormone therapy should not be used solely for cognition or for reduction of Alzheimer's Disease in the menopause.[146, 195(Level I), 196 (Level II-1)]

6.12 Menopausal Hormone Therapy and Skin

Collagen loss is highest during the first 5 years of menopause. Other age-related skin changes involve thinning of the epidermal and dermal skin layer, reduction in elastin content, decrease in skin moisture and an increase in wrinkles. These changes may be reversed by estrogen therapy.[198 (Level I), 199 (Level II-3)]

Topical facial estrogen (0.01% estrogen or 0.625 mg/gram of CEE cream) have shown to be beneficial to the skin and collagen layer. However, MHT is not recommended as first line therapy for the aging skin.[200 (Level II-2)]

1.	Collagen loss is highest in the first 5 years of menopause.[198 (Level I), 199 (Level II-3)]
2.	Estrogen therapy may reverse collagen loss, epidermal and dermal thickness layer, elastin content, skin moisture and wrinkles.[198 (Level I), 199 (Level II-3)]
3.	There are currently no recommendations for the use of menopausal hormone therapy for treatment of the aging skin.[200 (Level II-2)]

Recommendation 25
Menopausal hormone therapy is not advised as first line treatment for the aging skin.[200 (Level II-2)]

6.13 Menopausal Hormone Therapy and Hair, Dentition and Special Senses

6.13.1 Hair

MHT does not decrease menopause related hair loss or improve hair density. [201 (Level I), 202 (Level II)]

6.13.2 Dentition

The risk of gum disease in MHT users is reduced up to 44%.[203 (Level II-1)] The WHI study found that tooth loss was 24% lower in current MHT users than in nonusers.[204 (Level I)]

6.13.3 Vision

MHT has been shown to decrease the risk of cataracts and primary open angle glaucoma, however may increase symptoms of dry eyes.[77 (Level b), 205 (Level I), 206 (Level II-1)]

6.13.4 Voice Changes

MHT helps improve menopause related hoarseness of the voice. MHT users have a higher habitual pitch than non-users, especially in women with comparable BMI.[79, 207 (Level II-1)]

6.13.5 Hearing

Though conflicting data exists in preclinical models, MHT may play a role in hearing loss and olfactory changes.[208 (Level II-1)]

In small trials, it may decrease dizziness and improve postural balance.[209 (Level II-2), 210 (Level II-1)]

6.13.6 Smell

Olfactory test scores (odour identification, odour discrimination / memory, odour threshold sensitivity) were significantly higher in women receiving combined MHT than in past users and never users.[208 (Level II-1)]

6.13.7 Taste

MHT significantly improves blood flow in the salivary glands which then reduces the incidence of dry mouth. This can indirectly affect taste.[211 (Level II-2)]

1.	Menopausal hormone therapy does not decrease menopause related hair loss or improve hair density.[201 (Level I), 202 (Level II)]
2.	Menopausal hormone treatment has been shown to decrease gum disease and tooth loss, improve eyesight, hearing, smell, taste and decrease voice hoarseness; however, it is not recommended as first line treatment for these problems.[203 (Level II-1), 204 (Level I)]

Recommendation 26

Menopausal hormone therapy is not recommended as first line treatment for menopausal changes to hair, dentition, eyesight, hearing, smell, taste and voice.[201 (Level I), 202 (Level II), 203 (Level II-1), 204 (Level I)]

6.14 Menopausal Hormone Therapy and Breast

The most frequent cancer in women is breast cancer. Twelve percent of women who reach 90 years of age, develop breast cancer. The etiology of breast cancer is still poorly understood with known breast cancer risk factors attributing to only a small proportion of cases *(see Table 20)*. Over 80% of breast cancers in postmenopausal women occur in women who have never taken hormone therapy.[212, 213 (Level I)]

Table 20. Risk Factors for Developing Breast Cancer[213 (Level I)]

Non Modifiable Risks	Modifiable Risks
Getting older	Sedentary lifestyle
Genetic mutations (such as BRCA 1 & 2)	Overweight or obese especially after the menopause
Early menarche (before 12 years of age)	First pregnancy after the age of 30 years

Non Modifiable Risks	Modifiable Risks
Late menopause (after the age of 55 years)	Not breastfeeding
Having dense breasts	Nulliparity
Personal history of breast cancer, atypical hyperplasia or lobular carcinoma in situ	Increased alcohol consumption
Family history of breast cancer	Combined MHT (estrogen and progestogen)
Radiation treatment to the chest or breasts before the age of 30 years	
Women who were on diethylstilbestrol (DES) between 1940 –1971 to prevent miscarriages. Their daughters still carry a risk.	

(Source: Centres for Disease Control and Prevention, USA 2019)

Large observational studies have shown that the risk of breast cancer may vary with different doses and combinations of ET and EPT.[20 (Level I)]

In the New South Wales Cancer Lifestyle and Evaluation of Risk (CLEAR) study, current use of MHT (but not past use) is associated with a small increased risk of ER positive and ER and PR positive breast cancer. There is no increased risk seen with the other breast cancer subtypes.[214 (Level II-2)]

WHI investigators also found that women on EPT have an increased risk of abnormal mammograms, with a subsequent small increased risk of breast cancer.[215 (Level I)]

In 2020, the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) meta-analysis found a small increase in the absolute risk of breast cancer in MHT users.[216 (Level1)] The data was elaborated as follows:

5-year intake of MHT at the age of 50 years and risk of breast cancer at age 50 – 69 years.

For continuous combined MHT

Increase from a baseline risk of 3/50 women not on MHT to 4/50 (i.e. 1 extra case in 50 women)

For sequential combined MHT

Increase from a baseline risk of 4/70 women to 5/70 (i.e. 1 extra case in 70 women)

For estrogen only MHT

Increase from a baseline risk of 13/200 women to 14/200 (i.e. 1 extra case in 200 women)

10-year intake of MHT starting at the age of 50 years and risk of breast cancer at age 50 – 69 years

For continuous combined MHT

Increase from a baseline risk of 3/50 women not on MHT to 5/50 (i.e. 2 extra cases in 50 women)

For sequential combined MHT

Increase from a baseline risk of 4/70 women to 6/70 (i.e. 2 extra cases in 70 women)

For estrogen only MHT

Increase from a baseline risk of 13/200 women to 15/200 (i.e. 2 extra cases in 200 women)

The Joint Statement from the British Menopause Society (BMS), European Menopause and Andropause Society (EMAS), Royal College of Obstetrician and Gynaecologists (RCOG) and Australasian Menopause Society (AMS) in 2021, has strongly encouraged that the results of the CGHFBC meta-analysis not be taken in isolation and that the decision to take MHT should be individualised based on the woman's benefits and risks and improved quality of life with MHT. There was also no arbitrary limit to be placed on the dose or duration of usage of MHT.[217(Level1)]

Natural progestogens in the form of micronized progesterone and dydrogesterone are now seen to be the safer progestogens as they are associated with lower risk of breast cancer as compared to other synthetic progestogen.[218, 219 (Level II-2)] MHT use in the following women do not further increase the risk of breast cancer.

- Women with family history of breast cancer.[220 (Level I)]
- Women who are BRCA positive without breast cancer.[221 (Level I)]

In women who have undergone surgical menopause prematurely (bilateral oophorectomy), estrogen should be considered to decrease health risks without the fear of increased risk of breast cancer.[222 (Level I)]

The WHI study showed an increase in breast cancer in the EPT arm of the study. This risk was higher in previous users of menopausal hormone therapy and was not increased with family history of breast cancer. However, there was no increased risk of breast cancer for up to 7.2 years of estrogen only use in the ET arm of the WHI.[98 (Level I)]

In the 13 years follow up of the WHI data, hysterectomised women who received estrogen only in the form of CEE showed a non-significant reduction in breast cancer risk.[174 (Level I)]

The latest 18 year follow up of the WHI cohort showed that breast cancer mortality was not increased in both the EPT (HR 1.44, 95% CI, 0.97 -2.15) and ET users (HR 0.55, 95% CI, 0.33 – 0.92).[223 (Level I)]

In Malaysia, the risk of breast cancer is highest in the 40-to-60-year age group. [224 (Level II-2)]

A combination of a breast ultrasound and mammogram is ideal as a screening tool as breast tissue can be denser in younger women. Women on hormone replacement therapy should have their breast ultrasound repeated yearly and their mammogram every 2 years if the preceding results were normal.

MHT after breast cancer

The use of MHT after breast cancer is not advised. The results of various studies have been controversial, reporting either a neutral effect or an increased risk of breast cancer recurrence. [22(Level I), 226(Level III)]

MHT treatment for vasomotor symptoms may only be considered after a failed trial of non-hormonal therapy. A multidisciplinary team consisting of a menopause specialist, oncologist and gynaecologist should be present in the decision making and the benefits and risks individualised to that particular individual. The dose should be the lowest and for the shortest possible time. 226(Level III)

Breast cancer survivors with problems of GSM can safely use low dose vaginal ET without any fear of breast cancer recurrence, due to its minimal systemic absorption. 227(Level II-2) Local use of vaginal estriol and lactobacillus has also been studied in breast cancer survivors and has shown good safety profile. It is clinically effective in women with breast cancer on aromatase inhibitors.[228 (Level II-1)]

1.	The risk of breast cancer may vary with different doses and combinations of estrogen therapy and estrogen-progestogen therapy.[20 (Level I)]
2.	Hysterectomised women (women without a uterus) who received estrogen only therapy showed either a non-significant reduction or a very minimal increased risk of breast cancer which is relative to duration of use.[174, 216 (Level I)]
3.	Non-hysterectomised women who received the estrogen-progestogen combination showed a small increased risk which is relative to duration of use and type of progestogen used.[174,216 (Level I)]
4.	Current use, but not past user is associated with increased risk of ER positive breast cancer and ER and PR positive breast cancer.[214 (Level II-2)]
5.	Micronized progesterone and dydrogesterone when used as progestogen therapy in menopausal hormone therapy is associated with lowered risk of breast cancer.[218, 219 (Level II-2)]
6.	Menopausal hormone therapy does not alter the risk of breast cancer in women with family history of breast cancer or carry a positive BRCA gene mutation.[220,221 (Level I)]
7.	Use of menopausal hormone therapy after breast cancer is not advised, however low dose vaginal estrogen creams for symptoms of genitourinary syndrome of menopause, are permitted in breast cancer survivors.[227(Level II-2)]

Recommendations 27	
1.	Hysterectomised women (women without a uterus) with menopausal symptoms are treated with estrogen only therapy. There is a non-significant risk reduction or a very minimal increased risk of breast cancer which is relative to duration of hormone use.[174,216 (Level I)]
2.	Non-hysterectomised women (women with a uterus) with menopausal symptoms require an estrogen-progestogen combination. There is a small increased risk of breast cancer which is relative to duration of hormone use and type of progestogen used.[174,216 (Level I)]
3.	Menopausal hormone therapy may be recommended for symptomatic menopausal women who have a family history of breast cancer or carry a positive BRCA mutation.[220,221 (Level I)]
4.	Menopausal hormone therapy is not advised for breast cancer survivors.[22(Level I), 226(Level III)]

6.15 Menopausal Hormone Therapy and Other Cancers

6.15.1 Cervical Cancer

MHT use is not associated with an increased risk of cervical cancer. Post-hysterectomy, ET may be used for menopausal symptoms and does not increase the risk of cancer recurrence.[229 (Level II-2), 230(Level I)]

Menopausal hormone therapy use does not increase the risk of cervical cancer or recurrence of cervical cancer.[229 (Level II-2), 230(Level I)]

Recommendation 28	
	Women with menopausal symptoms may use menopausal hormone therapy (estrogen only) after a hysterectomy for treatment of cervical cancer.[229 (Level II-2), 230(Level I)]

6.15.2 Endometrial Cancer

In women with an intact uterus on MHT, addition of progestogen at an adequate dose *(see Table 9)* and duration is required for endometrial protection with no increased risk of endometrial cancer.[231, 232 (Level I)]

There is minimal evidence in the use of MHT after surgery for endometrial cancer due to its potential to stimulate any cells left behind at surgery. The benefits and risks of MHT use in such women should be individualised and weighed carefully.[233 (Level I)]

Menopausal hormone therapy is not advised after surgery for endometrial cancer as it has the potential of stimulating any cells that are left after surgery.[233 (Level I)]

Recommendation 29

Women with menopausal symptoms are not advised menopausal hormone therapy after endometrial cancer surgery due to fears of stimulating any remnant cancer cells.[233 (Level I)]

6.15.3 Lung Cancer

MHT use (either ET or EPT) is not associated with lung cancer. There is limited data that shows a reduction in lung cancer incidence; however this reduction is absent in smokers.[234, 235, 236, 237 (Level I)]

Menopausal hormone therapy does not increase the risk of lung cancer.
[234, 235, 236, 237 (Level I)]

Recommendation 30

Women with menopausal symptoms may use menopausal hormone therapy after lung cancer treatment.[234, 235, 236, 237 (Level I)]

6.15.4 Ovarian Cancer

The risk of ovarian cancer with long term MHT use has remained inconsistent across many studies.[238,239,240,241 (Level I)]

A significant association between combined MHT and ovarian cancer was not observed in the EPT arm of the WHI study (5.6 years follow up). In the estrogen only arm, there was an absolute risk of 4 cases with CEE alone versus 3 cases with placebo per 10000 person-years; this risk remained nonsignificant after a median 13 years follow up.[174 (Level I)]

A large meta-analysis of 52 epidemiological studies revealed one extra case of ovarian cancer per 1000 users and one extra ovarian cancer death per 1700 users who used MHT for 5 years from 50 years of age.[240 (Level I)]

Though data is limited, MHT use does not increase the risk of ovarian cancer in women with family history of ovarian cancer or in women with a BRCA mutation.[242 (Level I)]

There was no increased risk of recurrence or death in women receiving MHT after treatment of ovarian cancer.[243,244,245 (Level I)]

The risk of ovarian cancer with long term menopausal hormone therapy use has remained inconclusive.[238,239,240,241 (Level I)]

Recommendation 31

Menopausal hormone therapy (either estrogen only or estrogen progestogen combination) may be used for treatment of menopausal symptoms in women who have completed treatment for ovarian cancer.[174 (Level I)]

6.16 Menopausal Hormone Therapy and Quality of Life (QoL)

MHT has the following effects on QoL:

- A significant improvement in menopause-specific quality of life scores (MsQoL), mainly through relief of menopausal symptoms.[246, 247 (Level I)]
- An increase in sense of well-being in global quality of life scores (GQoL).[247, 248 (Level I)]
- MHT significantly relieves exhaustion, irritability, joint and muscle pain and vaginal dryness.[248 (Level I)]

Menopausal hormone therapy improves menopause-specific quality of life scores (MsQOL) and global quality of life scores (GQol).[246, 247, 247, 248 (Level I)]

Recommendation 32

Menopausal hormone therapy treatment for post-menopausal symptoms in women less than 60 years of age and within 10 years of menopause improves menopausal-specific quality of life scores (MsQOL) and global quality of life scores (GQol).[246, 247,247,248 (Level I)]

6.17 Menopausal Hormone Therapy, All-Cause Mortality and Global Index

In a cumulative 18 year follow up from WHI, use of menopausal hormone therapy for 5 – 7 years was not associated with risk of long-term all-cause mortality.[224 (Level I)]

The Global Health Index (an index of health status that combines all aspects of public health into a single number) has also shown to be favourable towards MHT use between 50 – 59 years.[175 (Level I)]

Table 21: Age specific risks for All-Cause Mortality with MHT use. Combined analysis of the two WHI trials.[175 (Level I)]

Age	Hazard Ratio (HR) for Death (All-causes) (95% CI)
50 - 59 years	0.70 (0.51 – 0.96)
60 - 69 years	1.05 (0.87 – 1.26)
70 – 79 years	1.14 (0.94 – 1.37)

Table 22: Age specific risks for Global Health Index with MHT use[175 (Level I)]

Age	Hazard Ratio (HR) for Global Index (95% CI)
50-59 years	0.96 (0.97 – 1.2)
60- 69 years	1.08 (0.89 – 1.13)
70 – 79 years	1.14 (0.02 – 1.29)

1.	The use of menopausal hormone therapy for 5 – 7 years was not associated with risk of long-term all-cause mortality.[224 (Level I)]
2.	The Global Health Index is favourable towards the use of menopausal hormone therapy in women between the ages of 50 – 59 years.[175 (Level I)]

Recommendation 33

Menopausal hormone therapy treatment for post-menopausal symptoms results in a more favourable global health index and a lesser all-cause mortality in women between the ages of 50 – 59 years.[175, 224 (Level I)]

Section 7: Menopausal Hormone Therapy (MHT) in Women with Special Problems

7.1 Menopausal Hormone Therapy and Endometriosis

Pre-menopausal women who have undergone bilateral salpingo-oophorectomy (removal of both tubes and ovaries) with or without a hysterectomy for endometriosis may experience exaggerated vasomotor symptoms due to the sudden decline in estrogen levels.

As endometriosis is an estrogen-dependent disease, the use of MHT in these women should be used with caution, as there can be reactivation of the endometriotic foci with a potential for malignancy. EPT is preferred rather than ET and can be considered if moderate to severe VMS is present.[249,250 (Level I)]

Treatment should be individualised based on age, disease severity, family history, co-morbidities and severity of symptoms. Evaluation of the risks and benefits of MHT use is carried out taking into consideration the possible resurgence of endometriosis and the small possibility of endometriosis related malignancy.[251 (Level I)]

Women with endometriosis who go on MHT after menopause should be regularly monitored with yearly pelvic ultrasounds. A biopsy is necessary in case of any suspicious recurrence.[250, 251 (Level I)]

Tibolone may be used as an alternative to estrogen progestogen therapy for treatment of menopausal symptoms.[256 (Level I)]

1.	Endometriosis is an estrogen dependent disease; menopausal hormone therapy should be used with caution in women with endometriosis due to possible reactivation of the endometriotic foci and the small possibility of endometriosis related malignancy.[251 (Level I)]
2.	Estrogen-progestogen treatment is preferred over estrogen only treatment for women who have had surgical menopause due to endometriosis.[249,250 (Level I)]

Recommendation 34	
1.	Women experiencing menopausal symptoms after surgical menopause due to endometriosis are advised an estrogen-progestogen combination due to fear of reactivation of endometriotic foci with estrogen only therapy.[251] (Level I)
2.	Tibolone may be used as an alternative to estrogen progestogen therapy for treatment of menopausal symptoms.[256] (Level I)

7.2 Menopausal Hormone Therapy and Fibroids

MHT is not contraindicated in menopausal women with fibroids. Annual pelvic ultrasounds are advised as MHT may increase the volume and size of asymptomatic fibroids. A low resistance pulsatility index (PI) in the uterine arteries in women with asymptomatic fibroids is associated with increased fibroid growth and can be used as a screening tool prior to initiating MHT.[252](Level II-3)

Tibolone may be used as an alternative in women with fibroids who require menopausal therapy.[252] (Level II-3)

1.	Menopausal hormone therapy is not contraindicated in women with fibroids, however it may increase the volume and size of asymptomatic fibroids.[252](Level II-3)
2.	Tibolone can be used as an alternative in women with fibroids who require menopausal hormone therapy.[253] (Level I)

Recommendation 35	
1.	Menopausal hormone therapy is not contraindicated in women with fibroids; however annual pelvic ultrasound examinations are advised to monitor the volume and size of fibroids.[252](Level II-3)
2.	Women with fibroids who experience menopausal symptoms may be offered tibolone as an alternative to menopausal hormone therapy.[253] (Level I)

7.3 Menopausal Hormone Therapy and Hypertension

Menopause by itself is a risk factor for hypertension and cardiovascular disease.[254] (Level I)

ET and EPT is not contraindicated in women with well-controlled blood pressure.[255] (Level I)

Menopausal hormone therapy is not contraindicated in women with well controlled blood pressure.[255] (Level I)

Recommendation 36

Menopausal hormone therapy can be recommended for treatment of menopausal symptoms in women with well controlled blood pressure.[255] (Level I)

Section 8: Tibolone

Tibolone is classified as a selective tissue estrogenic activity regulator (STEAR) as it activates hormonal receptors in a tissue specific manner. It acts similarly to a combined EPT preparation in treating menopausal symptoms.[256] (Level I)

The tissue specific effects of tibolone are:[256] (Level I)

- Estrogenic effects which relieve vasomotor symptoms. It has been shown to be favourable on the bone, brain and vagina.
- Progestogenic effects on the uterine endometrium preventing endometrial activity and hyperplasia.
- Androgenic effects by decreasing sex hormone binding globulin and increasing free testosterone. This improves libido and sexual activity.

Tibolone is used as follows:[256] (Level I)

- Women with an intact uterus with absence of periods for one year. If started earlier, unscheduled bleeding may occur.

- Women may transition from continuous combined MHT into tibolone therapy.
- Hysterectomised women may go on tibolone, or if the various estrogen preparations do not suit them.
- Women with special problems such as endometriosis or fibroids as it has been shown to have less effect on estrogen dependent growths.

Tibolone has been shown to be more effective than placebo and less effective than standard dose MHT in controlling vasomotor symptoms, in the Cochrane review involving 7 RCTs and 1657 women with moderate-quality evidence.[253] (Level I)

Tibolone decreases bone turnover and significantly improves bone mineral density. Over a period of 24 months, tibolone has been shown to decrease the risk of both vertebral fractures (HR 0.55, 95% CI, 0.41 to 0.74) and non-vertebral fractures (HR 0.74, 95% CI, 0.58 to 0.93). It also decreases the risk of invasive breast cancer (HR 0.32, 95% CI, 0.13 to 0.80) and colon cancer (HR 0.31, (95% CI, 0.10 to 0.96).[257] (Level I)

Women on tibolone may have unscheduled bleeding in the first 3 months of use which settles with time.[258] (Level I)

There is no evidence that tibolone increases the risk of endometrial cancer, VTE, cardiovascular events and mortality from any cause.[254, 258] (Level I)

Initiating tibolone after the age of 60 years is not advised as it can increase the risk of stroke. The LIFT study of tibolone for the prevention of bone loss and osteoporotic fractures showed an increase of 4 cases of stroke per 100 women in their fifties to 13 extra cases of stroke in women in their sixties.[258] (Level I)

Tibolone and its metabolites inhibit the formation of active estrogenic substances and promote the formation of inactive estrogen; it is thus associated with lesser breast density than conventional MHT preparations. Although tibolone does not increase breast mammographic density, regular breast surveillance is still recommended.[259] (Level I)

Tibolone is not advised in breast cancer survivors. The Liberate study which studied the effect of Tibolone on breast cancer survivors showed an increase in breast cancer recurrence.[259] (Level Ib)

1.	Tibolone has estrogenic, progestogenic and androgenic effects and is similar to a combined estrogen-progestogen preparation.[256] (Level I)
2.	Tibolone is effective in controlling vasomotor symptoms, decreases bone turnover and improves bone mineral density.[257] (Level I)
3.	Initiating tibolone after the age of 60 years is not advised as it can increase the risk of stroke.[258] (Level I)
4.	Tibolone is not advised in breast cancer survivors as it has been shown to increase breast cancer recurrence.[259] (Level Ib)

Recommendations 37	
1.	Post-menopausal women with menopausal symptoms may be offered tibolone as an alternative to estrogen or estrogen progestogen therapy.[256] (Level I)
2.	Tibolone may also be advised in post-menopausal women: • who are unable to tolerate menopausal hormone therapy and for whom sexual health issues and libido are the main areas of concern.[256] (Level I) • on continuous combined menopausal hormone therapy and want to transition into tibolone for long term use.[256] (Level I) • with endometriosis or fibroids who need menopausal treatment, as tibolone has less effect on estrogen stimulated growths.[256] (Level I)

Section 9: Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are compounds that exhibit tissue-specific estrogen receptor (ER) agonist or antagonist activity. SERMs work on estrogen receptors to either stimulate or negate the effect of estrogen.

SERMs comes under the umbrella of menopausal hormone therapy as it is used to treat post-menopausal osteoporosis. It is also used as an adjunct therapy by estrogen positive breast cancer patients due to its receptor antagonistic action. However, it may exacerbate vasomotor symptoms.

Common SERMs are:

- Tamoxifen is taken by breast cancer survivors to reduce breast cancer recurrence. Though it does help improve bone mineral density in post-menopausal women, it may stimulate the uterine endometrium due to its estrogen receptor (ER) agonist activity, increasing the risk of endometrial hyperplasia and malignancy.[260 (Level III)]

- Raloxifene (RLX) Hydrochloride (HCL) is a second generation SERM that was developed as an alternative to tamoxifen for the treatment and prevention of breast cancer.

The multicenter randomised placebo controlled, double blinded Multiple Outcomes of Raloxifene Evaluation (MORE) study was a three year study that looked at the use of raloxifene hydrochloride on the reduction in fractures in postmenopausal women with osteoporosis. With 60 mg of Raloxifene HCL, a 55% (95%CI, 0.3-0.7) reduction in new vertebral fractures in women without prior fractures and a 31% (RR 0.7, 95% CI 06,0.9) reduction in women with prior fractures was seen.[261 (Level I)]

Raloxifene decreased the risk of estrogen receptor-positive breast cancer by 90% (RR 0.10; 95% CI, 0.04-0.24), but not estrogen receptor-negative invasive breast cancer (RR, 0.88; 95% CI, 0.26-3.0). Among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with raloxifene.[262,263 (Level I)]

Raloxifene HCL is associated with a 3-fold increase in thromboembolic phenomenon. Other side effects include hot flashes, leg cramps, and peripheral edema.[263 (Level I)]

In 2002, Malaysia was part of the randomized, double-blinded, placebo-controlled study of the "Efficacy and Safety of Raloxifene 60 mg/day in Postmenopausal Asian Women" with its results published in 2003.[264 (Level I)] It was found that after six months of treatment with RLX HCL there was a:

- Significant decrease in bone markers (osteocalcin, N-telopeptide)

- Increase in lumbar spine BMD by 1.9%

- Significant decrease in total cholesterol by 5.3%

- A significant decrease in LDL by 7.7%

- Decrease in triglyceride levels by 1.56%

The incidence of adverse events like hot flashes and leg cramps were not significantly different from the placebo group.[264] (Level I)

In Malaysia, RLX HCL is mainly indicated for the treatment of postmenopausal osteoporosis and breast cancer recurrence.

1.	Selective estrogen receptor modulators (SERMs) come under the umbrella of menopausal hormone therapy as it is used to treat post-menopausal osteoporosis.[260] (Level III)
2.	Raloxifene hydrochloride over 3 years causes a 55% (95%CI, 0.3-0.7) reduction in new vertebral fractures in women without prior fractures and a 31% (RR 0.7, 95% CI 06,0.9) reduction in women with prior fractures.[261] (Level I)
3.	Raloxifene hydrocholoride over 3 years also decreased the risk of estrogen receptor-positive breast cancer by 90% but did not have an effect on estrogen receptor-negative invasive breast cancer.[262,263] (Level I)

Recommendations 38	
1.	Raloxifene hydrochloride is recommended for women with post-menopausal osteoporosis as it causes a 55% reduction in new vertebral fractures in women without prior fractures and a 31% reduction in women with prior fractures, when given over 3 years.[261] (Level I)
2.	Raloxifene hydrochloride may be recommended for women with post-menopausal osteoporosis who are at a higher risk for breast cancer as it has been shown to decrease estrogen receptor breast cancer by 90% when given over 3 years.[262,263] (Level I)

Section 10: Non-hormonal Management of Menopause

Women often explore alternative therapy for the treatment of menopausal symptoms due to the unwarranted fears of MHT use. The data supporting alternative therapy for treatment of menopausal symptoms is limited and remains inconclusive.

However, alternative treatment may be required for patients with a history of breast cancer and other medical disorders such as coronary artery disease, liver disease and previous thromboembolic episodes who suffer from specific symptoms of VMS and GSM.[130 (Level I)]

10.1 Pharmacological Therapy

Various pharmacological therapies have been used for vasomotor symptoms. [265 (Level I),266 (Level II-1)]

- Clonidine is an alpha-2 adrenergic agonist and an antihypertensive. It is the only licensed non-hormonal therapy in the United Kingdom for vasomotor symptoms. Clonidine and venlafaxine were found to be more effective than placebo when given to breast cancer survivors with hot flushes for over a period of twelve weeks.[266 (Level II-1)]

- Serotonin and noradrenaline reuptake receptor inhibitors (SNRIs) such as venlafaxine and desvenlafaxine.

  Venlafaxine at 100 mg / day given for a period of 52 weeks has been found to be an effective therapy for hot flushes when compared to placebo.[267(Level II-1)]

  In a short term 8 week study comparing venlafaxine with 17 beta estradiol; [268 (Level II-2)]

  - There was significant improvement in vasomotor symptoms with venlafaxine
  - 17 beta estradiol was superior in improving quality of life.
  - Both venlafaxine and 17 beta estradiol improved sleep quality.

- Serotonin selective reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, citalopram and escitalopram.

SSRIs and SNRIs have been shown reduce the frequency and severity of menopause-associated vasomotor symptoms by 10% to 64%. SSRIs like fluoxetine and paroxetine should be avoided in breast cancer patients taking tamoxifen as it diminishes its efficacy.[269] (Level I)

- Antiepileptics such as gabapentin and pregabalin.

  Gabapentin is an antiepileptic and used for neuropathic pain. A systematic review of 13 RCTs revealed that at a dose of 300 mg three times a day, it reduced the severity and frequency of vasomotor symptoms.[270] (Level II-1) At higher doses of 2400 mg daily, gabapentin was found to be as effective as conjugated equine estrogen in reducing VMS.[270] (Level II-1)

  Pregabalin, another anti-epileptic medication at 75 mg twice daily has also shown to significantly reduce the frequency and severity of vasomotor symptoms.[271] (Level II-1)

1.	Alternative therapy is offered to women with a history of breast cancer and other medical disorders such as coronary artery disease, liver disease and previous thromboembolic episodes who suffer from vasomotor symptoms but are unable to take menopausal hormone therapy.[130] (Level I)
2.	Alternative therapy such as clonidine, serotonin and noradrenaline reuptake receptor inhibitors (SNRIs), serotonin selective reuptake inhibitors (SSRIs) and antiepileptics have been shown to improve frequency and severity of vasomotor symptoms to a varying degree. 266,267,271 (Level II-1), 268 (Level II-2), 269 (Level I)

Recommendation 39

Symptomatic women with contraindications to the use of menopausal hormone therapy such as breast cancer and other medical diseases such as coronary heart disease, liver disease and previous thromboembolic episodes should be offered pharmacological therapy such as clonidine, serotonin and noradrenaline reuptake receptor inhibitors (SNRIs), serotonin selective reuptake inhibitors (SSRIs) and antiepileptics for the treatment of vasomotor symptoms.[130] (Level I)

10.2 Herbal Products

Isoflavones and phytoestrogen (nonsteroidal compounds that occur naturally in many plants, fruits, and vegetables that are structurally and functionally similar to estrogen) have not been found to be more efficacious than placebo in the treatment of VMS.

A systematic review of RCTs concluded that dietary and supplementary phytoestrogen may improve hot flushes and vaginal dryness but not night sweats. However, the quality of this evidence was poor.[272] (Level I)

Common isoflavones and phytoestrogen that have had well designed studies carried out on its effect on menopausal symptoms:

- Black cohosh. It has not been found to be useful in the treatment of menopausal symptoms.[273] (Level I) A potential safety concern would be its effect on breast cancer cells and possible hepatotoxicity if ingested in large volumes.[274, 275] (Level I)
- Red clover. Taking a probiotic together with red clover has been shown to reduce VMS when compared to placebo.[276] (Level I)
- Soy containing dietary supplements was associated with lower likelihood of VMS, (OR 0.63, 95% CI, 0.45–0.89), however it should be avoided in women with ER positive breast cancer.[277] (Level I)
- Chinese herbal therapy is ineffective for the treatment of menopausal hot flushes.[278] (Level I)
- Evening primrose oil (EPO) is believed to help treat hot flushes. In a placebo-controlled trial on 56 women for 6 months at 500mg per day there was no significant difference noted when compared to placebo.[279] (Level II-1)

Herbal supplements such as isoflavones and phytoestrogens have not been found to be more efficacious than placebo in the treatment of vasomotor symptoms.[272] (Level I)

Recommendation 40

Menopausal women experiencing vasomotor symptoms, are advised that the use of herbal supplements such as isoflavones and phytoestrogens for relief of symptoms may not be more efficacious than placebo.[274, 275 (Level I), 276 (Level I)]

10.3 Supplements

Supplements and their role in the menopause.

- Vitamin B. Deficiencies in any of the B vitamins can disturb the complex regulatory network and contribute to adverse health outcomes in the menopause such as cardiovascular disease, stroke, and dementia. Inadequate intake, malabsorption, interaction with medication and alcohol abuse may interfere with vitamin B absorption.[280 (Level I), 281 (Level II-3)]

- Vitamin E. 800 IU/day of Vitamin E has very little effect in reducing hot flushes.[282 (Level II-1)] When studied alongside gabapentin, Vitamin E was found to be less effective for hot flushes.[283 (Level II-1)]

- Calcium and Vitamin D supplementation is usually recommended for bone health. The requirements of calcium and vitamin D vary with age and gender.[284 (Level I)]

Women above the age of 51 years may need up to 1200 mgs of calcium daily (combination of dietary calcium and supplements). This had a positive effect on BMD as well as a modest effect on fracture risk reduction (RR 0.88; 95% CI, 0.83 – 0.95). [284 (Level II-3)]

Calcium carbonate absorption is better when taken with meals. However, absorption may be affected and side effects may be increased in women with gastric issues. In these patients, calcium citrate is better tolerated and absorped.[285, 286 (Level I)]

Calcium intake of 1000 mg daily (combination of dietary calcium and supplements) and Vitamin D, supplements have not been shown to increase all-cause or cardiovascular mortality.[287, 288 (Level I)]

One of the best sources of Vitamin D is through 15 – 30 minutes of direct sunlight exposure on the skin daily. Adequate supplementation of Vitamin D is recommended to reduce the risk of fractures and falls. Women below

the age of 70 years are recommended 600 IU of Vitamin D, whilst 800 IU is recommended for women over 70 years. Dark skin pigmentation can hamper the absorption of Vitamin D.[284,285 (Level I)]

The Institute of Medicine guidelines (2010) has stated that that the optimal serum 25(OH) vitamin D concentration to maintain skeletal health and reduce the risk of fractures and falls is 50 ng/mL Patients are at a risk for vitamin D deficiency at levels of less than 30 ng/mL.[285 (Level I)]

1.	Vitamin B deficiencies can contribute to adverse health outcomes in the menopause such as cardiovascular disease, stroke, and dementia.[280 (Level I), 281 (Level II-3)]
2.	In post-menopausal women, 1200 mgs of calcium (a combination of dietary sources and supplements) has a positive effect on bone mineral density and fracture risk reduction.[284 (Level II-3)]
3.	Adequate Vitamin D supplementation (600 IU in women below 70 years and 800IU after 70 years) reduces the risk of fracture and falls.[285 (Level I)]
4.	The optimum serum 25(OH) vitamin D concentration to maintain skeletal health with lesser risk of fractures and falls is 50 ng/mL. Risk of falls are higher with Vitamin D levels of less than 30 ng/mL. [285 (Level 1)]
5.	Calcium intake of 1000 mgs daily (combination of dietary calcium and supplements and Vitamin D supplements have not been shown to increases all-cause or cardiovascular mortality.[287, 288 (Level 1)]

Recommendations 41	
1.	1200 mgs of calcium (a combination of dietary sources and supplements) is recommended daily for its positive effect on bone mineral density and fracture risk reduction.[284 (Level II-3)]
2.	Adequate Vitamin D supplementation to achieve Vitamin D levels of more than 50 ng/mL is advised in order to maintain skeletal health and reduce the risk of fractures and falls.[285 (Level I)]

10.4 Alternative Therapy

Cognitive behavioural therapy is a goal-oriented psychotherapy that takes a hands-on practical approach to change patterns of behaviour and thinking. It can be used for anxiety, sleep issues and to improve mood in menopausal women. Relaxation techniques, sleep hygiene and enforcing a positive attitude is recommended to help ease VMS.[289] (Level I)

Hypnotherapy is often practised by menopausal women and has been shown to be useful.[289] (Level I)

There are no significant well conducted RCT's to show that stellate ganglion block, acupuncture, yoga, or exercise works for vasomotor symptoms.[94, 289, 290](Level I), 291 (Level II-1)

Alternative therapy such as hypnotherapy, cognitive behavioral therapy, relaxation techniques, sleep hygiene and enforcing positive attitudes have shown some beneficial on vasomotor symptoms, anxiety, sleep and mood.[289] (Level I)

Recommendation 42

Women experiencing menopausal symptoms may consider alternative therapy such as hypnotherapy, cognitive behavioral therapy, relaxation techniques, sleep hygiene and enforcing positive attitudes to help ease anxiety, sleep and vasomotor symptoms.[289] (Level I)

Section 11: Compounded Hormones

There is a clear distinction between compounded hormones and bioidentical hormones.

"Compounded hormones" are hormones which are custom made by a pharmacist based on a doctor's order. These hormones are not tested and approved by the Ministry of Health (MOH) and National Pharmaceutical Regulatory Agency (NPRA).

The term "bioidentical hormones" should be correctly used on hormones that are identical in molecular structure to endogenous hormones. Estradiol that is used in MHT is "bioidentical" while most compounded hormones are not "bioidentical".

Compounded hormones are not regulated and lacks standardization and quality control. There is lack of efficacy studies and labelling which should provide information on benefits and risks. This leads to concerns about safety, possibility of overdosing or under dosing.[292] (Level I)

There is currently no scientific evidence for prescribing compounded hormones over conventional menopausal hormone therapy.

There is currently no scientific evidence for prescribing compounded hormones over conventional menopausal hormone therapy due to the lack of safety and efficacy data.[292] (Level I)

Recommendation 43

Compounded hormones are not recommended for treatment of menopausal symptoms due to lack of safety and efficacy data.[292] (Level I)

Section 12: Body Identical Hormones

The word "body identical hormones" has been introduced to define exact duplicates of hormones which are usually synthesized by the human ovary and adrenal glands i.e., estradiol, estriol, estrone, progesterone, DHEA and testosterone. These hormones are seen as relatively safer hormones due its similarity of structure and behaviour to our own body hormones. Of these hormones, the progesterone body identical hormone is the most important. Micronised progesterone has been shown not to have an effect on the lipid and glucose metabolism and on vascular tone, fluid retention, weight gain and acne.[293 (Level I)]

Recent studies on the use of MHT in younger menopausal women have used body identical hormones such as the oral and transdermal estradiol and oral micronised progesterone. In these women, the risk of cardiovascular disease, stroke, VTE and breast cancer was not increased.[146(Level I), 217 (Level I)]

These hormones are considered safe and FDA approved.

1.	The word "body identical hormones" are precise duplicates of estradiol, estriol, estrone, progesterone, dehydroepiandrosterone acetate (DHEA) and testosterone hormones which are usually synthesized by the human ovary and adrenal glands.[293 (Level I)]
2.	The use of body identical hormones such as the oral and transdermal estradiol and oral micronised progesterone does not increase the risk of cardiovascular disease, stroke, VTE and breast cancer.[146, 217(Level I)]

Recommendation 44
Body-identical hormones are safe hormones due its similarity of structure and behavior to own body hormones. The use of oral and transdermal estradiol and oral micronised progesterone has not been shown to increase the risk of cardiovascular disease, stroke, venous thromboembolism and breast cancer.[146, 217(Level I)]

Section 13: Religious Perspectives

Malaysia is a multi–ethnic and a multicultural country. Many ethnic groups in Malaysia maintain separate cultural identities. This section will briefly deal with Islam, Christianity, Buddhism, and Hinduism. All religions welcome menopause positively and this section is to share the views of the various religions with regards to menopause.

Christianity

Christianity understands that the process of menopause is part of God's design and that the postmenopausal woman should emerge stronger, more assured, and content. Being older allows time for freedom for service. During the menopause transition period (which can be challenging), the Christian woman can turn to God's words for wisdom to help her and her family. The Christian woman can be assured that God will never leave her or forsake her. If she is married, the Christian woman should confide in her husband and communicate about her menopausal symptoms especially if she is not able to cope. In God's teachings, husbands are to love their wives and to cherish them always. Menopausal women should stay healthy and focus on overall health and not on body shape. She should exercise, not overeat, be in regular contact with her doctor and consider treatment like hormone therapy if she so needs it.[294 (Level II-3)]

Hinduism

Hinduism views the begininng and the end of menstrual cycles positively. When a girl gets her first menses, a celebration would be held by worshipping the Fertility Gods, and the girl be given gifts. Unfortunately the monthly menses is considered a taboo and she is not allowed to enter temples and to participate in any religious acts.[295 (Level II-3)] Many women in the reproductive age group take hormones to delay their periods if they need to attend temple ceremonies. Thus, menopause is a welcome sign for Hindu women. Women can now enter temples and are able to perform religious rituals. The menopause is celebrated as a period of freedom, experience, and wisdom. Taking MHT is not a contraindication as overall health is paramount.

Buddhism

In Buddhism, menopause represents a new phase of life. The menopausal woman undergoes an energetic, psychological and spiritual shift and is born as a "wise woman". During this period, Buddhism teaches women to revisit earlier parts of their lives that were left unexamined, or any wounds which

were left unattended. Buddhist women are taught that as the reproductive aspect of their physical body winds down, the spiritual aspects increase and would could continue to deepen for the rest of their lives. Menopause is much awaited for by the Buddhist woman.[296] (Level II-3)

Islam

Menopause is welcomed by the Muslim woman. The lack of monthly menstrual bleeding gives them the freedom to perform religious activities (BAK).

Aishah, the wife of the Prophet, once said that when women reached 50 years of age, they would be out of the menstrual age and would not deliver babies anymore.

In the Al-Quran, from Surah An-Nur states, "Such elderly women are past the prospect of marriage, there is no blame on them if they lay aside their (outer) garments, provided they make not wanton display of their beauty; but it is best for them to be modest; and Allah is One Who sees and knows all things."

This verse from the Quran refers to the older woman and menopause. They are free to perform their religious responsibilities for Allah knows and sees everything.

On 14th June 1998, the National Fatwa Council concluded on the following issues regarding MHT for menopausal women:[297] (Level III)

What is the Islamic perspective on menopause and HT?

- It is permissible to use MHT derived from the urine of pregnant horses. Characteristics of najis (colour, taste and smell) are removed after hormonal extraction.
- The transdermal method will prevent water from passing onto skin and must be removed before the bath cleaning from hadas (menstrual bleeding or after sex).
- Bleeding while on MHT is considered as hayd (menses) and thus all rules regarding menses apply.

Can women pray (and/or perform other religious activities) when there is vaginal bleeding (due to MHT)?

MHT is taken with the intention of taking care of their health so that they can perform their duties towards the husbands and families.[298] (Level III) Just like women with monthly menses before menopause, Muslim women cannot

perform religious activities like the solat or read the Quran if they have cylical bleeds while on MHT. The above religious rulings would apply.

"And they (women) have rights (over their husbands as regards living expenses) similar (to their husbands) over them (as regards obedience and respect) to what is reasonable." (Al-Baqarah: 228)[299] (Level III)

Permission from the husband is a must before starting on MHT. This is to avoid suspicion from the husband.

During the perimenopausal period, women sometimes face the problem of prolonged periods due to dysfunctional uterine bleeding (DUB). If a muslim woman continues to bleed beyond two weeks (14 days), they are allowed to perform the solat. They have to clean the vaginal area and cover it with a sanitary pad or cloth. They would then take the wudhuk (ablution) and perform the solat as soon as possible. They should do this everytime before solat. The doctor should be consulted to determine the cause of the abnormal bleeding so that the woman may receive the appropriate treatment.

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19.	Age specific risks for VTE with MHT use	66
20.	Risk factors for breast cancer	75
21.	Age specific risks for All-Cause Mortality with MHT use	84
22.	Age specific risks for Global Health Index with MHT use	84

Appendix 1

Example of Search Strategy

1. MENOPAUSE/
2. menopaus*.tw.
3. premenopaus*.tw.
4. PERIMENOPAUSE/
5. POSTMENOPAUSE/
6. (premature ovarian insufficiency).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. VASOMOTOR/
9. (hot flush).tw.
10. (climacteric symptom*).tw.
11. (genitourinary syndrom*).tw.
12. CARDIOVASCULAR DISEASES/
13. thromboembolism.tw.
14. (venous thromboembolism).tw.
15. osteoporosis.tw.
16. sarcopenia.tw.
17. mood.tw.
18. stroke.tw
19. metabolic.tw.
20. cognitive.tw.
21. skin.tw.
22. hair.tw.
23. dentition.tw.
24. t$$th.tw.
25. (special sense*).tw.
26. QOL/
27. (quality of life).tw.
28. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 7 and 28
30. lifestyle.tw.
31. 7 and 30
32. HORMONE REPLACEMENT THERAPY/
33. (menopaus* hormon* therapy).tw.
34. (hormon* replace* therapy).tw.
35. (hormon* therapy).tw.
36. MHT.tw.
37. HRT.tw.

38. 32 or 33 or 34 or 35 or 35 or 37
39. 7 and 38
40. 28 and 38
41. breast.tw.
42. cancer.tw.
43. ovarian.tw.
44. lung.tw.
45. colon.tw.
46. cervix.tw.
47. endometrium.tw.
48. 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 38 and 48
50. endometriosis.tw.
51. fibroid.tw.
52. hypertension.tw.
53. 50 or 51 or 52
54. 38 and 53
55. tibolone.tw.
56. (selective $estrogen receptor modulator).tw.
57. serms.tw.
58. 55 or 56 or 57
59. 7 and 58
60. THERAPEUTICS/
61. therap*.tw.
62. treatment*.tw.
63. herbal.tw
64. supplement*.tw.
65. (alternative therap*).tw.
66. (compound hormon*).tw.
67. 60 or 61 or 62 or 63 or 64 or 65 or 66
68. 7 and 67
69. religio*.tw.
70. 7 and 69

Appendix 2

Questions for Search Strategy Table

1. How is irregular bleeding during the perimenopause managed?

- local examination
- blood investigations
- radiological tests
- hormonal therapy

2. What would be the best treatment for women with premature ovarian insufficiency to prevent long term sequelae?

3. What is the most effective treatment for symptomatic menopausal women with the following problems?

- perimenopausal symptoms
- vasomotor symptoms
- mood disturbances
- genitourinary syndrome of the menopause
- osteoporosis and sarcopenia
- metabolic disorders
- skin
- cognition

4. What are the risks of menopausal hormone therapy to the following areas?

- cardiovascular disease
- venous thromboembolism
- stroke
- breast cancer
- other cancers

5. In which group of women should the following be used?

- oral menopausal hormone therapy
- non-oral menopausal hormone therapy
- vaginal estrogen therapy

6. What is the ideal menopausal hormone therapy for the following symptomatic women?

- women who have had a hysterectomy
- women with an intact uterus
- women who are perimenopausal and within 1 year of menopause
- women who are after 1 year of menopause
- obese women
- women with hypertriglyceridemia and active gall bladder disease
- women with known thrombophilia such as Factor V Leiden mutation
- women with higher risk of venous thromboembolism

7. What is the association of menopausal hormone therapy and breast cancer?

- With estrogen only use
- With estrogen and progestogen use
- In women with breast cancer
- In women with family history of cancer

8. Is there a mandatory time limit for menopausal hormone therapy use?

9. What is the role of the following in treating menopausal symptoms?

- Tibolone
- SERMs
- Non-hormonal management

Appendix 3

Menopause Questionnaire

Developed by the Working Committee of the Clinical Practice Guidelines for Menopause Management in Malaysia

This simple guideline is aimed to help health care workers to evaluate a woman going through the menopausal change and to track their progress with lifestyle changes, non-hormonal therapies and menopausal hormone therapy.

Symptoms vary in every woman. The symptomatology chart serves to objectively evaluate a woman during hormonal or non-hormonal treatment.

Date:_____

Name: _____ Age: _____

NRIC / Passport: _____

Height: _____Weight: _____ BMI: _____

Last known period:_____Period cycles: regular / irregular

Number of children:_____ Last child birth:_____ Miscarriages:_____

1. Have you had any gynaecological problems before?

- o Fibroids
- o Adenomyosis
- o Ovarian cysts
- o Heavy periods
- o Others: If yes, please specify _____

2. Have you had any surgery on your uterus or ovaries? _____
   If yes, please specify _____

3. Do you have any of these medical problems?

- o High blood pressure
- o Diabetes
- o High cholesterol levels
- o Coronary heart disease
- o Cancer
- o Blood clotting problems
- o Others: If yes please specify_____

4. Are you on any medication?

If yes, please specify_____

5. Is there a family history of the following?

- o High blood pressure
- o Diabetes
- o High cholesterol levels
- o Coronary heart disease
- o Cancer
- o Blood clotting problems
- o Others: If yes, please specify _____

6. Are you on any of the following supplements?

- o Multivitamins
- o Fish Oil
- o Calcium
- o Vitamin D
- o Herbal supplements for menopause
- o Others: If yes, please specify_____

7. Would you be willing to consider menopausal hormone therapy if needed?

_____

Please indicate if you are bothered by any of these symptoms and to what extent.

0 = Not at all
1 = It bothers me a little
2 = I am bothered by these symptoms
3 = These symptoms are interfering with my quality of life

Symptoms	0	1	2	3
Irregular periods (period intervals which are shorter or longer)				
Hot flushes				
Night sweats (sweating at night)				
Weight gain (especially at midriff)				
Abdominal bloating				
Sleeping problems				
Palpitations (stronger & loud heart beat)				
Tiredness (unable to do normal daily activity)				
Loss of head hair				
More hair over the face				
Change in skin texture				
Joint and muscle pains				
Heaviness in the head				
Headaches				
Breathing difficulties				
Moody and feeling down				
Anxiety				
Fogginess (forgetfulness)				
Concentration problems				
Feeling tense and nervous				
Loss of interest in many things				
Crying spells				
Irritability				
Dry skin				
Vaginal dryness or irritation				
Loss of interest in sex				
Bleeding with sexual activity				
Increase in urinary tract or vaginal infections				

Appendix 4

OSTA Osteoporosis Self-Assessment Tool for Asians [89] (Level I)

Osteoporosis Self-Assessment Tool for Asians (OSTA)

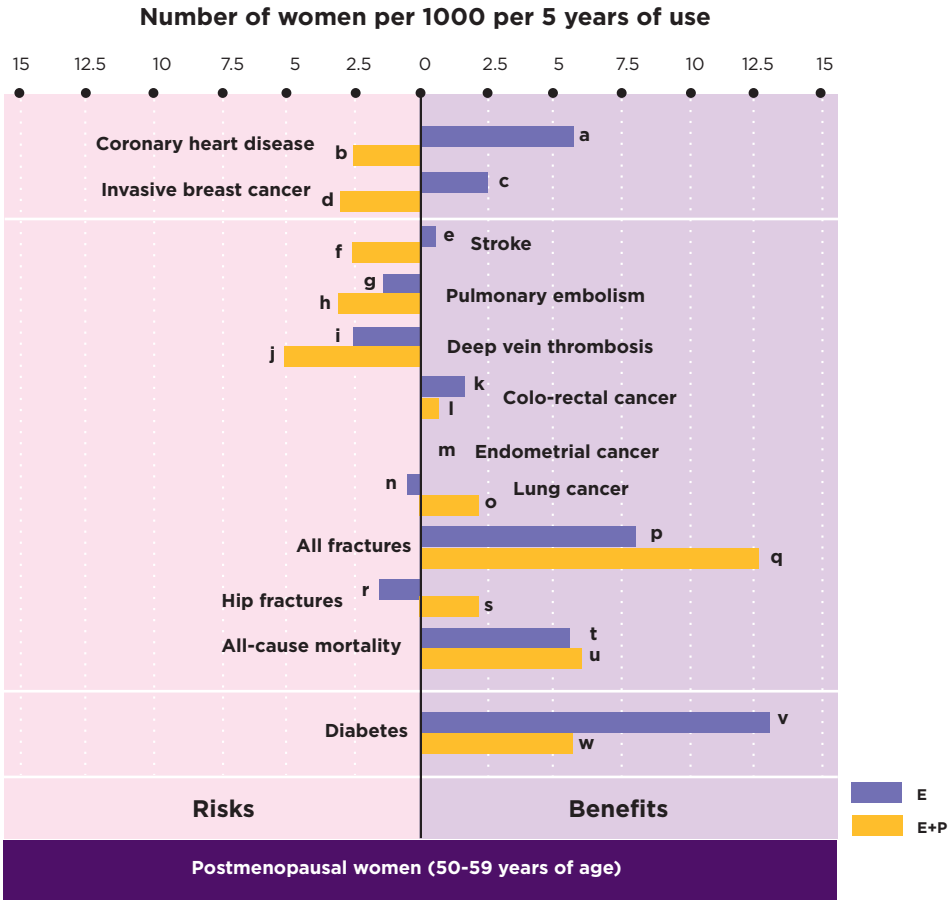
Age (Yr)	Weight (kg)							
	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
45-49								
50-54								
55-59						Low Risk		
60-64								
65-69			Moderate Risk					
70-74								
75-79								
80-84	High Risk							
85-89								

Appendix 5

Benefits and Risks of MHT use in women aged 50 – 59 years

Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50 to 59 years during intervention phase of WHI. In women between 50 – 59 years of age.[131 (Level I)]

E: estrogen; E+P: estrogen-progestin;



Section 5.6 (Benefits and Risks) refers to the above chart with detailed explanation of the effect of MHT on various parameters in Section 6.

Appendix 6

The Types of MHT preparations

Continuous Estrogen

Estrogen

No tablet break
No bleeding as no uterus

Sequential HRT

Estrogen

Progestogen

Day 14 — Sequential therapy without tablet break
Regular bleeding at end of cycle

Continuous Combined HRT

Estrogen
Progestogen

Day 14 — Combined therapy without tablet break
No bleeding at end of cycle

(Source: de Villiers, T.J. et al. (2013). Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric.[16(3), 316-37) 97 (Level Ib)]

D. Abbreviations

Abbreviation	Description
AD	Alzheimer's Disease
AFC	Antral Follicle Count
AMH	Anti-Müllerian Hormone
AUB	Abnormal Uterine Bleeding
AMS	Australasian Menopause Society
BMD	Bone Mineral Density
BMI	Body Mass Index
BMT	Bone Turnover Markers
BMS	British Menopause Society
BTB	Breakthrough Bleeding
CPG	Clinical Practice Guidelines
CEE	Conjugated Equine Estrogen
CHD	Coronary Heart Disease
CI	Confidence Interval
CLEAR	New South Wales Cancer Lifestyle and Evaluation of Risk
COC	Combined Oral Contraceptives
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CVD	Cardiovascular Disease
DES	Diethylstilbestrol
DHEA	Dehydroepiandrosterone Acetate

Abbreviation	Description
DG	Developmental Group
DM	Diabetes Mellitus
DOPS	Danish Osteoporosis Prevention Study
DVT	Deep Vein Thrombosis
DUB	Dysfunctional Uterine Bleeding
EMA	European Medicines Agency
EMAS	European Menopause and Andropause Society
EPO	Evening Primrose Oil
ER	Estrogen Receptor
ET	Estrogen Therapy
EPT	Estrogen and Progestogen therapy
FIGO	International Federation of Gynaecology and Obstetrics
FSFI	Female Sexual Function Index
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practice
GQoL	Global Quality of Life
gm	gram (s)
GSM	Genitourinary Syndrome of the Menopause
HABITS	Hormonal Replacement Therapy After Breast Cancer-Is It Safe?
HCL	Hydrochloride

Abbreviation	Description
HDL	High Density Lipoprotein
HMB	Heavy Menstrual Bleeding
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HT	Hormone Therapy
i.e.	That is
IMS	International Menopause Society
IU	International Units
KEEPS-Cog	Kronos Early Estrogen Prevention Cognitive and Affective Study
LDL	Low Density Lipoprotein
LNG-IUS	Levonorgestrel Intrauterine System
Lp(a)	Lipoprotein A
MetS	Metabolic Syndrome
mg	milligram(s)
mcg	microgram (s)
MHT	Menopausal Hormone Therapy
MOH	Ministry of Health
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	Medroxy Progesterone Acetate

Abbreviation	Description
MsQoL	Menopause-Specific Quality of Life
ng/ml	nanograms per milli litres
nmol/L	nanomoles per Litre
NHMS	Malaysian National Health and Morbidity Survey
25 (OH)	25 hydroxy
NPRA	National Pharmaceutical Regulatory Agency
PAI-1	Plasminogen Activator Inhibitor-1
PALM-COEIN	Polyps, adenomyosis, leiomyoma, malignancy, coagulation disorders, ovulatory dysfunction, endometrial causes, iatrogenic cause and not otherwise classified.
PE	Pulmonary Embolism
PI	Pulsatality Index
PMS	Pre Menstrual Symptoms
POI	Premature Ovarian Insufficiency
QoL	Quality of Life
RC	Review Committee
RCOG	Royal College of Obstetrician and Gynecologists
RCT	Randomised Control Trial
RLX	Raloxifene
RG	Review Group
RR	Relative Risk

Abbreviation	Description
SERMs	Selective Estrogen Receptor Modulators
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin and Noradrenaline Reuptake Receptors
STEAR	Selective Tissue Estrogenic Activity Regulator
STRAW	Stages of Reproductive Aging Workshop
Tab	Tablet (s)
TIA	Transient Ischemic Attack
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
VHIS	Vaginal Health Index Score
VMI	Vaginal Maturation Index
VMS	Vasomotor Symptoms
VTE	Venous ThromboEmbolism
WHI	Women's Health Initiative
WHO	World Health Organisation

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