



ACADEMY OF  
MEDICINE OF MALAYSIA



COLLEGE OF OBSTETRICIANS  
& GYNAECOLOGISTS

# HORMONE THERAPY DURING MENOPAUSE IN MALAYSIAN WOMEN



MINISTRY OF  
HEALTH MALAYSIA



MALAYSIAN MENOPAUSE  
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OF MALAYSIA



**COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS**  
**Academy of Medicine of Malaysia**

# **Clinical Practice Guidelines**

on

## **“ Hormone Therapy during Menopause in Malaysian Women ”**

### **Collaborating agencies**



Ministry of Health Malaysia



Malaysian Menopause Society



Obstetrical & Gynaecological  
Society of Malaysia



Academy of Family Physicians  
of Malaysia

( MOH/P/PAK/207.10(GU) )

# **CLINICAL PRACTICE GUIDELINES**      on

## **HORMONE THERAPY DURING MENOPAUSE IN MALAYSIAN WOMEN**



A project of the  
College of Obstetricians & Gynaecologists  
Academy of Medicine of Malaysia

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# **FOREWORD**

Hormone Therapy (HT) remains the most effective option for menopausal symptoms. There are many good clinical data to indicate that the use of HT started in early menopause is effective and safe.

Despite all this, both doctors and the public are still apprehensive and anxious about its continued use. Prevailing misconceptions and misinterpretations about HT may be contributed by several factors, including cultural practices, social mores, misinformation through media, and differing practices of medical personnel based on inconsistent scientific data. Access to information through unmonitored media and internet has to some extent, contributed to confusing information playing down the value of good scientific facts.

The HT users and prescribers have opened themselves to such influences. What they really need to do is to broaden their knowledge of the menopause and its treatment and assess its appropriateness in the light of recent scientific evidence.

The results of the Women's Health Initiative (WHI) study has initially raised anxiety on HT use for the menopause, but it is prudent to refer to the many international criticisms of this study, and its relevance only to certain age groups with allied clinical profiles.

It is therefore timely to re-look at the current evidence available and see how scientific data will impact on HT use in Malaysian postmenopausal women. The production of these Clinical Practice Guidelines (CPG) is largely based on review of such data and acceptable clinical practice.

The CPG Committee has carefully deliberated on much of the available scientific data to come out with various Consensus Statements and the CPG. Input has also been given by invited non-gynaecology experts in the areas of bone, cardiovascular and breast health. To further make this document credible, local and international reviewers have been invited to critically review the document before its final print.

The CPG Committee is made up of representatives from the College of Obstetricians & Gynaecologists, Malaysia, the Obstetrical & Gynaecological Society of Malaysia, the Malaysian Menopause Society, the Academy of Family Physicians of Malaysia, and the Ministry of Health of Malaysia, under the auspices of the College of Obstetricians & Gynaecologists, Academy of Medicine of Malaysia.

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## **COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS**

### **Academy of Medicine of Malaysia**

#### **Clinical Practice Guidelines on**

#### **“Hormone Therapy during Menopause in Malaysian Women”**

## **I. TITLE**

The title of this document is

**HORMONE THERAPY DURING MENOPAUSE IN MALAYSIAN WOMEN.**

## **II. BASIS FOR DEVELOPMENT OF THIS CPG**

Hormone Therapy (HT) has been the mainstay for treatment of menopause. When the results of the Women’s Health Initiative (WHI) study were published in 2002 and 2004, concerns were raised about the safety of HT use and this caused anxiety and concern to both medical professionals and the public.

There are, currently, many new research evidences available, especially on the safe use of HT in early menopause.

The College of Obstetricians & Gynaecologists, Academy of Medicine of Malaysia, in line with its academic aspirations, decided to produce an updated Clinical Practice Guidelines (CPG) in the hope that this would benefit medical practitioners in Malaysia when faced with the issue of menopause treatment in their clinical practice.

The College enlisted other relevant agencies to participate in this venture, namely the Obstetrical & Gynaecological Society of Malaysia, the Malaysian Menopause Society, the Academy of Family Physicians of Malaysia, and the Ministry of Health Malaysia.

The CPG Committee was tasked with deliberation of the available scientific data. Experts in the areas of bone health, cardiovascular health and breast health were invited to give their input, and evaluation of the final document by local & international assessors was sought to lend credibility to this document.

### **III. CLINICAL QUESTIONS ADDRESSED**

When considering the use of HT in postmenopausal women, medical practitioners may have important questions on their minds.

Such questions include:

- what are the clinical benefits of HT ?
- what are the risk situations in HT use ?
- who would benefit from HT ?
- when to start HT ?
- how does one prescribe HT ?
- what are the dose regimes ?
- is there a time limit to its use ?
- who cannot use HT ?

This Clinical Practice Guidelines will serve to answer many of the above questions, and allow the medical practitioner more confidence in the clinical use of HT in their practice.

### **IV. TARGET GROUP**

This CPG was developed for medical practitioners in Malaysia who are involved in the management of postmenopausal women.

### **V. TARGET POPULATION**

This CPG was developed for the safe use of estrogen therapy and estrogen-progestin therapy for postmenopausal women in Malaysia.

### **VI. PROCESS**

1. This CPG Committee was established by the College of Obstetricians & Gynaecologists, Academy of Medicine of Malaysia on September 3, 2008.
2. Representation into this committee was sought from the Malaysian Menopause Society, the Obstetrical & Gynaecological Society of Malaysia, the Academy of Family Physicians of Malaysia, and the Ministry of Health Malaysia.
3. The first meeting of the CPG Committee was held on 22-02-09, and altogether the committee has had 7 monthly meetings.

4. Initially, during the meetings, the committee members looked at various scientific evidence related to various parameters pertaining to the menopause, and how hormone therapy affected these.
5. Scientific evidence was obtained through review of current medical literature on hormone therapy and menopause using search engines available online.

( The search engines include Yahoo Search, Medline, e Medicine, Google, WebMD, Search Medica, MdLinx.ObGyn, Medscape.OB/GYN, DocGuide, ORGYN.com, websites of the International Menopause Society, North American Menopause Society, British Menopause Society, Australasian Menopause Society. )

( Key words used in the searches – menopause, menopause-heart disease, -VTE, -stroke, -vagina, -quality of life, -sexuality, -urinary tract, -breast cancer, -menopausal symptoms, -depression, -sleep, -skin, -bone health, -colon cancer.)

The committee looked at mainly meta-analysis, systematic reviews, randomized controlled trials, longitudinal cohort studies, and others.

International guidelines on the subject were also referred to.

6. Levels of evidence and grades of recommendation used in this CPG follow that of the SIGN50 criteria, revised edition 2008, Reference 82 in the list of references. The details of the SIGN50 criteria are enclosed in this CPG document.

These were applied to the section on “ Clinical Benefits of Hormone Therapy ” and the list of References.

7. During the course of the meetings, experts in the areas of cardiovascular, bone and breast health during menopause were invited to participate in the discussions.
8. The draft copy of this CPG was then produced by the CPG Committee, and circulated to all its members for scrutiny and feedback comments.  
Following this, the final draft copy was produced.

9. The final draft copy was then sent to 2 local reviewers for their comments. These comments were reported to the CPG Committee at its last meeting on 27-09-09, and further modifications were made.
10. The modified final draft copy was then sent to 2 international reviewers and their comments sought.
11. After receiving the international reviewers comments, the CPG document was then prepared
12. The CPG document was then sent to the Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia for assessment.
13. The CPG Committee had agreed that this CPG will be reviewed in 3 years time and any new data pertaining to the subject matter of this CPG will be reviewed, discussed, and modifications made to the CPG wherever necessary.

No pharmaceutical company has been directly involved in the preparation, discussion and finalization of this document.

The CPG Committee wishes to emphasise that this document serves as a guideline for clinical practice in the use of HT for menopause in Malaysian women. When in doubt, readers should re-look at the references quoted and after re-evaluation of the data, act appropriately for their patient's benefit.

# APPENDIX I

## **Levels of evidence & Grades of recommendation according to the SIGN50 criteria, updated 2008**

(Reference 82)

### **Key to evidence statements and grades of recommendations**

#### **LEVELS OF EVIDENCE**

- 1 ++ High quality meta-analysis, systematic review of RCTs, or RCTs with a very low risk of bias
  
- 1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
  
- 1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias
  
- 2++ High quality systematic reviews of case control or cohort studies  
  
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
  
- 2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
  
- 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not casual
  
- 3 Non-analytic studies, eg case reports, case series
  
- 4 Expert opinion

## GRADES OF RECOMMENDATION

*Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.*

<b>A</b>	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
<b>B</b>	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++or 1+
<b>C</b>	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
<b>D</b>	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

## GOOD PRACTICE POINTS

(√) Recommended best practice based on the clinical experience of the guideline development group



## **VII. OBJECTIVES**

### **Overall Objective**

The overall objective is to improve the effectiveness and efficiency of clinical care in the area of hormone therapy for menopause through the identification of evidence-based good clinical practice and desired clinical outcomes.

### **Specific Objectives**

1. To provide medical practitioners in Malaysia with a working knowledge of the clinical benefits and risks of the use of hormone therapy, i.e. estrogen therapy (ET) and estrogen-progestin therapy (EPT) for female menopause.
2. To provide medical practitioners in Malaysia with practical working guidelines on the use of ET and EPT for female menopause.

## **VIII. DEFINITIONS**

The following definitions will be used in this document:

### **Menopause**

Menopause is a state of natural ovarian senescence with accompanying estrogen deficiency. It also refers to states of ovarian failure and ovarian destruction/removal with accompanying estrogen deficiency.

### **Premature Menopause ( 15, 96, 97 )**

This refers to menopause in a woman aged below 40 years.

### **Early Menopause**

This refers to menopause in a woman aged 50 years to 59 years.

### **Late Menopause**

This refers to menopause in a woman aged 60 years and over.

**Surgical menopause** refers to menopause occurring as a result of surgical removal of both ovaries in a woman.

**Medical menopause** refers to menopause occurring as a result of permanent damage to both ovaries in a woman following either chemotherapy or radiotherapy.

( NB. Women with either surgical or medical menopause can be allocated to one of the menopause groups above. )

**Hormone Therapy (HT)**

This refers to the use of estrogens (ET), estrogens plus progestins (EPT) and androgens (AT).

**Estrogen-Progestin Therapy (EPT)**

This refers to therapy with estrogen in combination with a progestin. This term is synonymous with the term “hormone replacement therapy” (HRT).

**Estrogen Therapy (ET)**

This refers to therapy with estrogens alone. This term is synonymous with the term “estrogen replacement therapy” (ERT).

**Standard Dose ET & EPT\***

Essentially this refers to the dose of estrogen in the preparation, viz,

- Conjugated equine estrogens 0.625mg
- Estradiol valerate 2.0mg

**Low Dose ET & EPT\***

Essentially this refers to the dose of estrogen in the preparation, viz,

- Conjugated equine estrogens 0.30mg or 0.45mg
- Estradiol valerate 1.0mg

( NB \* for the actual preparations available, please refer to APPENDIX II and other relevant drug compendiums for details )

**IX. DIAGNOSIS OF MENOPAUSE**

The diagnosis of menopause is mainly clinical, viz

**a. Clinical Criteria**

1. age around menopause ( around 50 years )
2. no periods for 12 months
3. menopausal symptoms

( NB. All 3 clinical criteria need not be present for a diagnosis )

Laboratory diagnosis is generally not necessary for the diagnosis of menopause. However, where in doubt, laboratory testing of FSH may support the diagnosis, viz

**b. Laboratory Criterion**

1. FSH level > 35miu/ml

(NB. estradiol levels can be tested for, but this is not required for the establishment of diagnosis. )

**X. CLINICAL BENEFITS OF HORMONE THERAPY**

The following benefits of hormone therapy have been reported by scientific studies:

(NB Grades of recommendations – A to D, follow the SIGN50 criteria, reference 82, Appendix I )

**a. VASOMOTOR SYMPTOMS**

**Hot Flashes**

1. ET and EPT are effective in reducing the **frequency** of hot flashes. ( 1, 3-5, 12-13,18, 25, 30, 32 )
2. ET and EPT are effective in reducing the **severity** of hot flashes  
( 1, 3-5,12-13,18, 25, 30,32 )
3. Low-dose ET and EPT are also effective in reducing the frequency and severity of hot flashes. ( 1, 3-5, 18, 25 )

**Sweats / Night Sweats**

1. ET and EPT are effective in reducing the **frequency** of sweats, including night sweats. ( 2, 3, 4, 30 )
2. ET and EPT are effective in reducing the **severity** of sweats, including night sweats. ( 2, 3, 4, 30 )
3. Low-dose ET and EPT are also effective in reducing the frequency and severity of sweats, including night sweats.  
( 2, 3, 4, 30 )

## **Evidence Statements**

- i) Low-dose and standard dose ET are effective for relief of hot flushes and/or sweating. (1+)
- ii) Low-dose and standard dose EPT are effective for relief of hot flushes and/or sweating. (1+)

## **Recommendation**

- i) Menopausal hot flushes and/or sweating are indications for the use of ET and EPT. ( A )

## **b. VAGINA**

- 1. ET and EPT increase the vaginal maturation index and relieve vaginal atrophy. ( 1, 3, 5, 18, 51, 54, 55 )
- 2. ET and EPT reduce vaginal dryness. ( 3, 5, 51, 52, 53 )  
EPT reduces the incidence of vaginal pain, dyspareunia, vaginal discharge, and burning sensation. ( 49 )
- 3. The above effects are also seen with low-dose ET and EPT. ( 1, 3, 5, 18, 45 )
- 4. There is better relief of vaginal symptoms and greater improvement in cytological findings with topical vaginal estrogen therapy compared to oral estrogen therapy. ( 51, 52, 54 )
- 5. Daily and twice weekly use of low dose estrogen cream was equally effective in relieving symptoms of vulvo-vaginal atrophy. ( 99 )

## **Evidence statements**

- i) Low-dose and standard dose ET are effective in relieving vaginal atrophy, and its related symptoms, e.g. vaginal dryness and dyspareunia ( painful coitus ). (1+)

- ii) Low-dose and standard dose EPT are effective in relieving vaginal atrophy, and its related symptoms, e.g. vaginal dryness and dyspareunia ( painful coitus ). (1+)
- iii) The use of vaginal estrogen products for the treatment of atrophic vaginitis is well-documented. (1+)
- iv) Low dose vaginal estrogen therapy is also effective in relieving symptoms of vaginal atrophy. (1+)

### **Recommendation**

**i) Vaginal dryness due to vaginal atrophy during menopause is an indication for the use of ET and EPT. ( A )**

### **c. URINARY SYSTEM**

1. EPT reduces the incidence of lower urinary symptoms, e.g. dysuria, frequency of micturition, nocturia. ( 3, 18, 49, 50, 52, 53, )

**NB.** However, with regards to urinary incontinence, stress and urge incontinence, most studies indicate that these conditions are not benefited by ET and EPT, Instead ET and EPT use may worsen the above conditions. ( 12, 13, 50 )

### **Evidence statements**

- i) EPT is effective for relief of lower urinary tract symptoms related to estrogen deficiency. (1+)
- ii) Most studies show that in postmenopausal women with urinary incontinence, ET and EPT are not beneficial and may worsen the condition. (1+)

### **Recommendation**

**i) Lower urinary tract symptoms due to estrogen deficiency during menopause are indications for the use of ET and EPT. ( A )**

#### **d. DEPRESSIVE MOOD**

1. ET and EPT are effective in reducing depressive mood. The same effect is seen with low-dose ET and EPT. ( 3, 4, 6, 18, 30, 32 )

##### **Evidence statements**

- i) Low-dose and standard dose ET are effective in relief of mood disorders, especially depressive mood. (1+)
- ii) Low-dose and standard dose EPT are effective in relief of mood disorders, especially depressive mood. (1+)

##### **Recommendation**

- i) Depressed mood during menopause is an indication for the use of ET and EPT. ( A )

#### **e. SLEEP**

1. EPT reduces the incidence of difficulty in sleeping, sleep disturbances, and sleep problems. ( 2, 3, 4, 5, 32, 33 )
2. ET decreases the sum of time spent awake during sleep, and increases the total time spent in rapid-eye-movement sleep. ( 34 )
3. Sleep improvements with EPT may, however, be secondary to reduction in hot flushes. ( 4 )

##### **Evidence statement**

- i) ET and EPT are associated with improved sleep patterns and less sleeplessness. (1+)

##### **Recommendation**

- i) Sleep disturbance related to menopause, particularly sleeplessness, is an indication for the use of ET and EPT. ( A )

## **f. SKIN**

1. EPT improves various parameters associated with skin aging, namely, decreases dryness, increases hydration, elasticity and skin thickness. ( 22, 23 )

### **Evidence statement**

- i) **EPT use improves skin health during menopause. (1+)**

### **Recommendation**

- i) **Improvement of skin health per se is not an indication for the use of EPT. ( ✓ )**

## **g. BONE**

1. ET and EPT increase bone mineral density ( BMD ) at both the hip and vertebral spine. ( 7, 9, 11, 18, 27 )  
This response is dose-related for the vertebral spine. ( 18, 27 )
2. Low dose EPT plus calcium supplements is more effective in increasing BMD compared to EPT alone. ( 18, 27 )
3. ET and EPT reduce bone turnover, as evidenced by bone turnover markers. ( 11, 18 )
4. EPT reduces the risk of vertebral and non-vertebral ( hip & lower arm ) fractures. ( 7, 8, 9, 10, 11, 12, 18, 27, 98 )
5. The effect of EPT on non-vertebral fractures is greater in women below 60 years of age compared to those 60 and above. ( 27 )
6. ET reduces the risk in women of having any arthroplasty, hip and knee arthroplasty, while EPT reduces the risk of any arthroplasty except for the hip. ( 29 )

### **Evidence statements**

- i) **Low-dose and standard dose ET are effective in increasing bone mineral density (BMD), and reducing bone turn-over. (1+)**

- ii) **Low-dose and standard dose EPT are effective in increasing bone mineral density (BMD), reducing bone turnover, and reducing the incidence of both vertebral and non-vertebral fractures. (1+)**

### **Recommendations**

- i) **ET and EPT are first-line choices for the prevention of bone loss in post-menopausal women. ( A )**
- ii) **ET and EPT are first-line choices for the prevention of fractures in post-menopausal women who have increased risk for fractures. ( A )**

NB The term “first-line choice” is not synonymous with “indication”. In the context of bone health, besides HT, other first-line choices include calcitonin, bisphosphonates, and raloxifene.

### **h. SEXUALITY**

1. ET and EPT improve various aspects of female sexuality.
2. ET and EPT increase sexual desire, sexual arousal, sexual activity & its frequency, frequency and intensity of orgasm, sexual responsiveness, and overall sexual satisfaction. ( 36, 37, 45 )

ET and EPT also decrease the incidence of sexuality problems. ( 37 )

3. The addition of testosterone to ET and EPT significantly further improves on the female sexuality issues mentioned above. ( 39, 43, 44, 46, 47 )

One study showed that the use of testosterone alone improves on sexuality in postmenopausal women. ( 38 )

### **Evidence statements**

- i) **ET and EPT improves female sexual desire, sexual activity and overall sexual satisfaction in post-menopausal women. (1+)**



- ii) Testosterone supplementation of ET and EPT further improves various aspects of sexual function in post-menopausal women. (1+)

**Recommendations**

- i) Decreased sexual functioning during menopause is not a primary indication for the use of ET and EPT, but is a key factor to be considered. ( √ )
- ii) Testosterone therapy in post-menopausal women with sexual problems is not universally accepted and should be used with caution. ( √ )

**i. HEALTH-RELATED QUALITY OF LIFE**

Health-Related Quality of Life ( HR-QOL ) measures includes domains like vasomotor symptoms & mood changes, physical symptoms (sleep, uro-genital symptoms, skin changes), psycho-social aspects, and sexuality issues.

1. Overall, EPT improves HR-quality of life by its positive effects on the above quality of life measures.
2. Some studies indicate that EPT improves many domains of HR-QOL ( 4, 35, 48, 49 ).
3. Other studies indicate that EPT improves various aspects of HR-QOL namely, mental health and depressive symptoms ( 6 ), and physical functioning, bodily pain, and sleep ( 2 )

**Evidence statements**

- i) EPT use improves overall health-related quality of life. (1+)
- ii) In essence, ET and EPT, by their positive effects on the clinical benefits outlined above, definitely improve overall health-related quality of life. (1+)

## **Recommendation**

- |                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>i) <b>Health-related Quality of Life issue, is, in itself, not a primary indication for the use of EPT, but is a key-factor to be considered. ( ✓ )</b></p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

### **j. COLO-RECTAL**

1. ET use is associated with a reduction in the risk of colo-rectal cancer ( 24, 40, 41, 42 ).
2. EPT use is associated with a reduction in the risk of both invasive colon cancer ( 26, 40, 41, 42 ) and rectal cancers ( 26, 41 ).
3. Some studies show the longer the duration of use of ET and EPT, the higher the reduction in risk ( 24, 42 ), while others do not show this ( 40, 41 ).
4. ET and EPT use are also associated with a reduction in the risk of fatal colon cancer ( 40 ).

### **Evidence statement**

- i) **ET and EPT use are associated with reduced incidences of colon and rectal cancers. (1+)**

## **Recommendation**

- |                                                                                                             |
|-------------------------------------------------------------------------------------------------------------|
| <p>i) <b>Prevention of colon / rectal cancers is not an indication for the use of ET and EPT. ( ✓ )</b></p> |
|-------------------------------------------------------------------------------------------------------------|

## **XI HORMONE THERAPY & OTHER SYSTEMS**

### **a. CORONARY HEART DISEASE**

1. Overall, ET and EPT use are associated with a lower total mortality rate in postmenopausal women, including mortality from coronary heart disease. ( 12, 13, 57 )

2. In **late** menopausal women,
  - i)* EPT is associated with an increased risk of coronary heart disease. ( 12, 57 )
  - ii)* With ET, there is no increased risk ( 13 )
3. In **early** menopausal women,
  - i)* EPT is associated with a decreased risk of coronary heart disease ( 57, 58, 60 )
  - ii)* With ET, there is no increased risk. ( 13, 58, 59, 63 )
4. Considering **timing of initiation**
  - i)* When EPT is initiated within 10 years following onset of menopause, there is no increased risk of coronary heart disease ( 56, 58, 60 )
  - ii)* When EPT is initiated after 10 years or more following onset of menopause, there is an increased risk of coronary heart disease ( 56, 58, 60 )
5. Studies show that ET and EPT are not to be used for either the primary or secondary prevention of coronary heart disease. ( 61, 62 )

### **Evidence statements**

- i) ET use is not associated with any increase in risk of coronary heart disease. (1+)**
- ii) EPT use is not associated with an increase in risk of coronary heart disease when used in post-menopausal women in early menopause, and if started within 10 years of menopause. (1+)**
- iii) EPT use is associated with an increase in risk of coronary heart disease when used in post-menopausal women in late menopause, and if started after 10 years of the menopause. (1+)**

## **Recommendations**

- i) It is not recommended that ET or EPT be used for the primary prevention of coronary heart disease in postmenopausal women.  
This is the current cautious approach and guideline. ( A )**
  
- ii) It is not recommended that ET or EPT be used for the secondary prevention of coronary heart disease in postmenopausal women. ( A )**

### **b. Venous Thrombo-Embolism ( VTE )**

1. ET and EPT increase the risks of VTE at least by 2-3 fold ( 12, 13, 64, 65, 66, 67, 89, 92 ).
2. With EPT, the risk of VTE has been shown to increase in women with other risk factors for VTE, e.g. increasing age, over-weight, obesity, presence of factor V Leiden mutation. ( 64, 65, 92 )
3. With ET, VTE risk has been shown not to be increased further in women by age, BMI or presence of other risk factors for VTE. ( 92 )
4. With EPT, the risk is highest with the first year of use. ( 64, 67, 89, 92 ) and remains high for at least 5 years. ( 92 )
5. With ET, the risk has been shown to be greatest in the first 2 years, and remains elevated after this. ( 92 )
6. Use of oral estrogens increases the risk of VTE. ( 64, 66, 67, 92 )
7. Use of transdermal estrogens does not appear to increase the risk of VTE ( 64, 66, 67, 92 ), and has been shown not to confer additional risk in women at high risk of VTE. ( 67 )

### **Evidence statements**

- i) Oral ET and EPT use are associated with increased risks of VTE. (1+)
- ii) Transdermal estrogens do not appear to increase the risk of VTE. (1+)

### **Recommendations**

- i) Oral EPT should not be used in post-menopausal women who have a history of VTE or who are at high risk for VTE. In such women, transdermal EPT should be considered. ( A )
- ii) Oral ET should not be used in post-menopausal women who have a history of VTE. In such women, transdermal ET should be considered. ( A )

### **c. STROKE**

1. ET and EPT increase the risk of stroke. ( 12, 13, 58, 60, 89, 90, 91 )
2. ET increases the risk of ischaemic stroke in generally healthy postmenopausal women, and this risk is present in all subgroups of women, including younger and more recently menopausal women. ( 91 )
3. Two studies showed that there is no increase in risk if HT is used for less than 5 years in younger postmenopausal women. ( 58, 68 )

### **Evidence statement**

- i) ET and EPT use are associated with increased risk of stroke. (1+)

### **Recommendation**

- i) ET and EPT are not to be used in postmenopausal women with high risk for stroke. ( A )

## **d. BREAST**

### **ET use**

1. Overall, there is no increase in risk of breast cancer with the use of ET ( 13, 70, 71, 74, 75, 77, 78 ). The WHI study showed that this is true up to 7.1 years of use ( 13 ), while other studies showed no increased risk up to 15 years ( 70, 95 ), and even up to 20 years of use. ( 75, 78 )
2. For ductal cancers, studies showed, overall, that there is no increase in risk, even after 20 years of use of ET. ( 75, 76, 78 ). Any increase in risk of ductal cancer was entirely restricted to lean women with BMI < 25. ( 69, 75, 78 )
3. For lobular cancers, one study showed that there is an increased risk after 10 years of ET use. ( 78 )
4. One study showed that there was a statistically significant increase in risk of estrogen receptor and progesterone receptor positive cancers after 15 years of ET use. ( 75 )

### **EPT use**

1. Overall, with the use of EPT, there is an increase in risk of breast cancer. The WHI study showed that this increase in risk is seen after 5 years. ( 12 ). In other studies, the increased risk is seen after the first 2- 3 years of use. ( 69, 70, 71, 73, 76, 77, 78, 79, 80 )
2. There is a suggestion that the increase in risk of breast cancer is for lobular cancer, and not for ductal cancer. ( 71, 73, 76 )
3. The increase in risk of breast cancer with EPT use was seen to be higher in the following situations:
  - \* in lean women with BMI <25 ( 69 )
  - \* in estrogen-receptor positive cancers ( 73 )
4. While some studies show that there is no increase in risk with the use of transdermal EPT, ( 72, 77 ) others show no difference in risk between oral vs transdermal estrogens. ( 74, 79 )

5. Some studies show that the relative risk of breast cancer is not affected by a family history of breast cancer or other risk factors. ( 12, 72 )

### **Other data**

1. Studies of use of HT in women with a family history of breast cancer showed no increase in breast cancer risk. ( 94 )
2. There is no increased breast cancer risk in women with a history of benign breast condition. ( 94 )
3. There is no contraindication for the use of HT in women with fibrocystic mastopathy. ( 93 )
4. While previous small observational studies showed no increase risk of recurrence from the use of HT in breast cancer survivors, one RCT showed a recurrence hazard ratio of 3.3. ( 94 )

### **Evidence statements**

- i) Oral EPT increases the risk of breast cancer, especially lobular cancer. (1+)**
- ii) Transdermal EPT may not increase the risk of breast cancer. (2-)**
- iii) ET does not increase the risk of breast cancer. (1+)**

### **Recommendations**

- |                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"><li><b>i) HT can safely be used in women with history of benign breast conditions. ( A )</b></li><li><b>ii) HT may be used for menopausal symptoms in a woman at increased risk of breast cancer with appropriate counseling and surveillance. ( B )</b></li><li><b>iii) Unless more evidence shows otherwise, it is prudent not to use HT in breast cancer survivors. ( B )</b></li></ol> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## **XII PATIENT PERSPECTIVES**

It is relevant to take into account patient perspectives when considering hormone therapy for the postmenopausal woman. This will give insight to the medical practitioner as to how best to counsel the patient. The following conclusions are derived from a Malaysian survey and surveys from other international communities. (*please refer to references 83 – 88 in the “References” list*)

1. The top 3 most common menopausal symptoms experienced by Malaysian women are sleeplessness, headache and reduced sex drive. Nevertheless, the experience of menopausal symptoms can be quite varied in different populations.

It is also seen that the more negative the attitude to menopause and aging, the more likely is the woman to report presence of symptoms.

2. In general, Malaysian women feel that menopause does affect their life somewhat, the greatest impact coming from symptoms such as joint aches and pains, followed closely by lack of physical fitness.
3. The menopause experience in women is worse when associated with perception of losses in life, e.g. loss of childbearing capacity, loss of culture, threatened loss of children.

Menopause experience seems to focus on the difficult experiences a woman undergoes in relation to family life and work experiences.

4. Data shows that Malaysian women are not well informed about menopause in general, but they agree slightly that severe menopausal symptoms need to be treated.

Overall, postmenopausal women are poorly informed about the menopause, and they also have a poor understanding of it. Low awareness of HT is associated with its low prevalence of use.



5. Some of the most common sources of information that Malaysian women use or have ever used to get information on menopause are magazines, and newspapers, and the most sought-after people for information are acquaintances and family doctors.

However, it has been shown that doctors and health-care professionals provide little information about HT.

Nevertheless, women do have a genuine desire for more information about menopause and its treatment.

6. HT is not the most common treatment for menopausal complaints. For those who are currently using HT or had ever used HT, they have a somewhat positive feeling about HT.

In Malaysia, only about 10% of postmenopausal women are taking HT, while 30-40% are on herbal remedies.

Headache is the main menopausal symptom that prompted most Malaysian women to seek treatment.

7. For Malaysian women who are on HT for their menopausal symptoms, the gynaecologist is the influencer to most women in starting HT.

Most women perceive HT only for short-term relief of symptoms, rather than for its long-term benefits.

European women also believe that HT is good for the prevention of osteoporosis.

8. Only 8% of women had stopped using HT once, and they were advised by their family doctor to stop on medical grounds.

Other reasons for stopping HT include side-effects, concern about long-term health, e.g. breast cancer and VTE, disappearance of menopausal symptoms, and weight gain.

9. The main benefit women associate with HT use is alleviation of symptoms, and the main risk associated with HT is developing breast cancer.

In western countries, women also include prevention of osteoporosis as a benefit.

10. Though most women have somewhat positive feelings about HT in general, there is a significant number of women who are not aware of the benefits and consequences of using HT.

Overall, women have both positive and negative benefits about HT.

Women were more likely to use HT if they have symptoms.

11. The number one hurdle for women to start using HT is the fear of breast cancer, and belief that HT cannot alleviate the symptoms.

Studies show that the reasons for refusal to start taking HT include: belief that menopause is a natural event, hence, there is no need for any treatment; that HT is unnatural and with potential dangers; HT was never recommended to them; their doctor was against HT use.

12. Data shows that gynaecologists and doctors can be the main influencer of using HT.

On the other hand, it has also been shown that most of the women were not recommended to use HT by their doctors.

In never-users, one reason for not using HT is that HT was never offered to them.

### **XIII CLINICAL PRACTICE GUIDELINES**

The following Clinical Practice Guidelines have taken into account, available scientific evidences and existing consensus statements & guidelines of various international agencies.

In addition to data and information from the references listed under "References", the following documents have also been referred to in the preparation of this section:

- i) Position Statement by the Executive Committee of the International Menopause Society, " Guidelines for the hormone treatment of women in the menopausal transition and beyond " *February 13, 2004*
- ii) Guidelines for hormone replacement therapy of Asian women during the menopausal transition and thereafter, *Delfin Tan et al, 2006, Climacteric, 9: 146-151*

- iii) IMS Updated recommendations on postmenopausal hormone therapy, *Amos Pines et al, 2007, Climacteric, 10: 181-194*
- iv) Asia-Pacific Menopause Federation Consensus Statement on the management of the menopause, *April 2008*
- v) Position Statement of the North American Menopause Society on Estrogen and progestogen use in postmenopausal women : *July 2008*
- vi) British Menopause Society Council Consensus Statement on Hormone Replacement Therapy, “Hormone replacement therapy : Managing the menopause”. *February 2008*
- vii) SOGC Clinical Practice Guideline, *January 2009*
- viii) The Practice Committee of the American Society for Reproductive Medicine, “Estrogen and progestogen therapy in postmenopause”  
*Fertility & Sterility, 2006, 86 suppl 4, pages S75-S88*
- ix) Evidence-based review of therapies at the menopause  
*Alastair H MacLennan, 2009, 7: 112-123*

## **1. Holistic Approach to Menopause Management**

HT should be part of an overall approach to the management of menopause. Other aspects of management include lifestyle modifications, proper diet, regular exercise, cessation of smoking and avoidance of alcohol abuse.

## **2. Indications for HT**

HT should only be recommended when there is a definite and clear indication. Indications can be classified as:

- i) presence of symptoms
- ii) the need for prevention of osteoporosis

**Indications** for the use of HT include the following situations in relation to menopause:

- i)
  - a. Relief of vasomotor symptoms ( hot flushes and/or sweating )
  - b. Relief of joint and muscle aches and pains.

c. Relief of sleeplessness and other sleep disturbances

NB In Asian women, joint and muscle aches and pains, and sleeplessness are the commonest complaints in postmenopausal women.

d. Relief of depressed mood

e. Relief of uro-genital symptoms, particularly vaginal dryness

f. Relief of sexual dysfunction, including decreased libido

g. Maintaining and improvement of quality of life

NB Quality of life and sexuality are key factors to be considered in the management of the aging individual.

ii)

a. As one of the first-line choices, for the prevention of bone loss in postmenopausal women.

b. As one of the first-line choices, for the prevention of fractures in postmenopausal women who have increased risk for fractures. (This should be weighted against other available non-estrogen medications for the same purpose.)

NB The initiation of HT for the sole purpose of prevention of fractures is not recommended in women over 60 years of age.

### **3. Counselling and Decision-Making**

Each woman should be counseled on current data regarding the risks vs benefits of HT in simple terms; informed about the potential side-effects, and any special concerns applicable to her particular situation before starting HT.

Explanation on risks should be made in absolute numbers as this would be more appropriate rather than in percentages or relative risks, as follows:

<b>* WHI ( 2002 ) Absolute risks of EPT ( ref 12 )</b>		New cases	Additional absolute risks
<b>heart disease</b>	<b>7</b>	<b>7 / 10,000</b>	<b>7 / 10,000</b>
<b>stroke</b>	<b>8</b>	<b>8 / 10,000</b>	<b>8 / 10,000</b>
<b>breast cancer</b>	<b>8</b>	<b>8 / 10,000</b>	<b>8 / 10,000</b>
<b>VTE</b>	<b>18</b>	<b>18 / 10,000</b>	<b>18 / 10,000</b>
<b>pulmonary embolism</b>	<b>8</b>	<b>8 / 10,000</b>	<b>8 / 10,000</b>

<b>* WHI ( 2004 ) Absolute risks of ET ( ref 13 )</b>		New cases	Additional absolute risks
<b>heart disease</b>	<b>-5</b>	<b>-5 / 10,000</b>	<b>-5 / 10,000</b>
<b>stroke</b>	<b>12</b>	<b>12 / 10,000</b>	<b>12 / 10,000</b>
<b>VTE</b>	<b>7</b>	<b>7 / 10,000</b>	<b>7 / 10,000</b>
<b>breast cancer</b>	<b>-7</b>	<b>-7 / 10,000</b>	<b>-7 / 10,000</b>

One should also take into account the woman’s own preferences and expectations.

Only after this, can the woman make an informed, individual decision on whether or not she would want to take HT.

#### **4. Pre-treatment Evaluation**

This should include taking a medical history, relevant family history, doing a physical examination including weight, height, BMI, blood pressure and breast examination.

Where possible, a bimanual vaginal examination and cervical cytology should be done.

Relevant investigations can be considered, either laboratory or imaging - these are not mandatory. These include mammography / sonography, cardiovascular risk profiles including lipid profile, diabetes screening, full blood count etc.

Mammography should be undertaken according to age and national guidelines.

Assessment of bone mineral density (BMD) should be considered on a case-to-case basis.

Other tests may be done on a case-to-case basis, e.g. liver function tests, thyroid profiles, ultrasonography of the pelvis.

## **5. Contra-indications**

Contra-indications to HT should be ruled out before starting HT. These include the following:

- history of breast cancer
- history of VTE or stroke
- undiagnosed uterine bleeding
- significant cardiovascular disease
- hypersensitivity to estrogen.

## **6. Timing of Initiation**

Initiation of HT should be done in relation to proximity to menopause. Thus, it is best to start HT between the ages of 50-59 years, or within 10 years of the menopause.

After the age of 60 years, HT should not be initiated unless there is a compelling indication.

For those with premature menopause, HT should be recommended and started as soon as possible.

## **7. Dosages**

As a principle, the lowest effective dose of estrogen consistent with treatment goals should be used, with a corresponding low dose of progestogen.

Low-dose HT has been shown to be as effective as standard-dose HT for most of the indications mentioned above, and hence, should be the first-line choice.

Lower doses of progestogen will have less negative effect on breast cancer risk. For women with premature menopause, higher doses of estrogen may be required for relief.

## **8. Addition of progestogen**

In a woman with an intact uterus, progestogen is added to systemic estrogen.

This provides endometrial protection from unopposed estrogen and prevents the occurrence of endometrial hyperplasia and carcinoma.

Progestogens should be given for 12-14 days for every 28 days of estrogen (cyclical), or it can be given together with estrogen on a daily basis (continuous).

When using low-dose vaginal estrogen for relief of uro-genital atrophy, there is no necessity for added progestogen.

Progestogen supplementation is also not generally required in a woman who has had a hysterectomy, and who is on ET.

### 9. Dose Regimes

There are multiple dosing regime options especially for endometrial safety when adding progestogen to estrogen (EPT). There are also multiple dosing regimes when using ET.

For ET, estrogens can be given as standard or low dose, viz:

<b>estrogen</b>	<b>standard dose</b>	<b>low dose</b>
conjugated equine estrogen	0.625mg	0.3mg
17β estradiol valerate	2.0mg	0.5mg – 1.0mg
micronised estradiol	1.0 – 2.0mg	0.25 – 0.5mg
transdermal estradiol	50-100mcg	25mcg

For EPT, progestogens should be added to the estrogen doses above, viz:

<b>progestogen</b>	<b>standard dose</b>	<b>low dose</b>
medroxyprogesterone acetate	2.5 – 5.0mg	1.5mg
norethindrone acetate	1.0 – 2.0mg	0.1 – 0.5mg
drospironone	2.0mg	0.5mg
micronised progesterone	100mg	50mg

The dose and regime of HT need to be individualized.

This is the key to successful use of HT to provide health benefit with minimal risks, thereby enhancing quality of life.

Older postmenopausal women generally require lower doses than younger women.

### 10. Routes of administration

These include oral and transdermal routes.

Transdermal routes include the patch, gel and implant.

There is currently no symptomatic benefit of one route of administration over the other for systemic ET. Both oral and non-oral routes have advantages and disadvantages.

Transdermal routes have the advantage of avoiding the first-pass liver effect, and may be more favourable than oral routes, especially with regard to VTE and cardiovascular risks.

### **Estrogen administered vaginally**

When used for the treatment of vulvo-vaginal symptoms, consideration should be given to the use of local vaginal products.

The use of vaginal estrogen products for the treatment of atrophic vaginitis is well documented.

Creams have the advantage over tablets in their ability to be applied directly to the vulva and vulvo-vaginal area and provide flexibility in dosing and frequency of administration. The most widely prescribed local vaginal therapy for vaginal atrophy is conjugated equine estrogens ( CE ) cream.

Studies have shown the effectiveness of CE cream in reducing the sign of atrophic vaginitis as measured by effects on the vaginal maturation index ( VMI ).

Even the use of low dose vaginal estrogens, given daily or twice weekly have proven effective for the same purpose.

### **11. Duration of use**

There is no mandatory limitation to the duration of HT use, especially when HT is started during the menopause transition, and the woman is symptom-free on HT.

HT should be given for as long as the woman wants, if the lowest effective dose is used; the woman is aware of the potential benefits and risks; and there is clinical supervision.

HT can be considered even in the absence of symptoms where there is a genuine need for further prevention of osteoporotic fractures and/or preservation of bone mass in women with osteopenia when alternative therapies are not appropriate.



## **12. Follow-up Assessment & Frequency**

Annual risk-benefit assessment should be carried out.

The same procedures as in the “Counselling” visit and the “Pre-Treatment Evaluation” should be considered.

Timely mammography is the key, including genital tract cancer studies, e.g. cervical cytology and other investigations.

A 12-monthly follow-up assessment is recommended.

As for mammography, if the initial mammogram is normal, 2-3 yearly mammography is recommended.

## **13. Premature menopause**

Women with premature menopause should be considered as a group with special needs compared to those with natural menopause.

Special counseling in various areas needs to be addressed.

Premature menopause is associated with a lower risk of breast cancer, but with a higher risk and earlier onset of osteoporosis and cardiovascular disease.

HT should be started as soon as possible.

HT is to be continued until the typical natural normal age of menopause.

Higher doses of HT may be required in these women for symptom relief.

The risks of HT attributable to these young women are likely to be smaller and the benefits potentially greater than those in older women.

Nevertheless, the merits of long-term use of HT need to be assessed for each individual at regular intervals.

## **Conclusion**

Besides the role of life-style modifications and dietary adjustments in the prevention of menopause-related disease, HT ( hormone therapy ) remains a principal tool in preventing menopause-related illnesses and maintaining quality of life in the post-menopausal woman.

## APPENDIX II

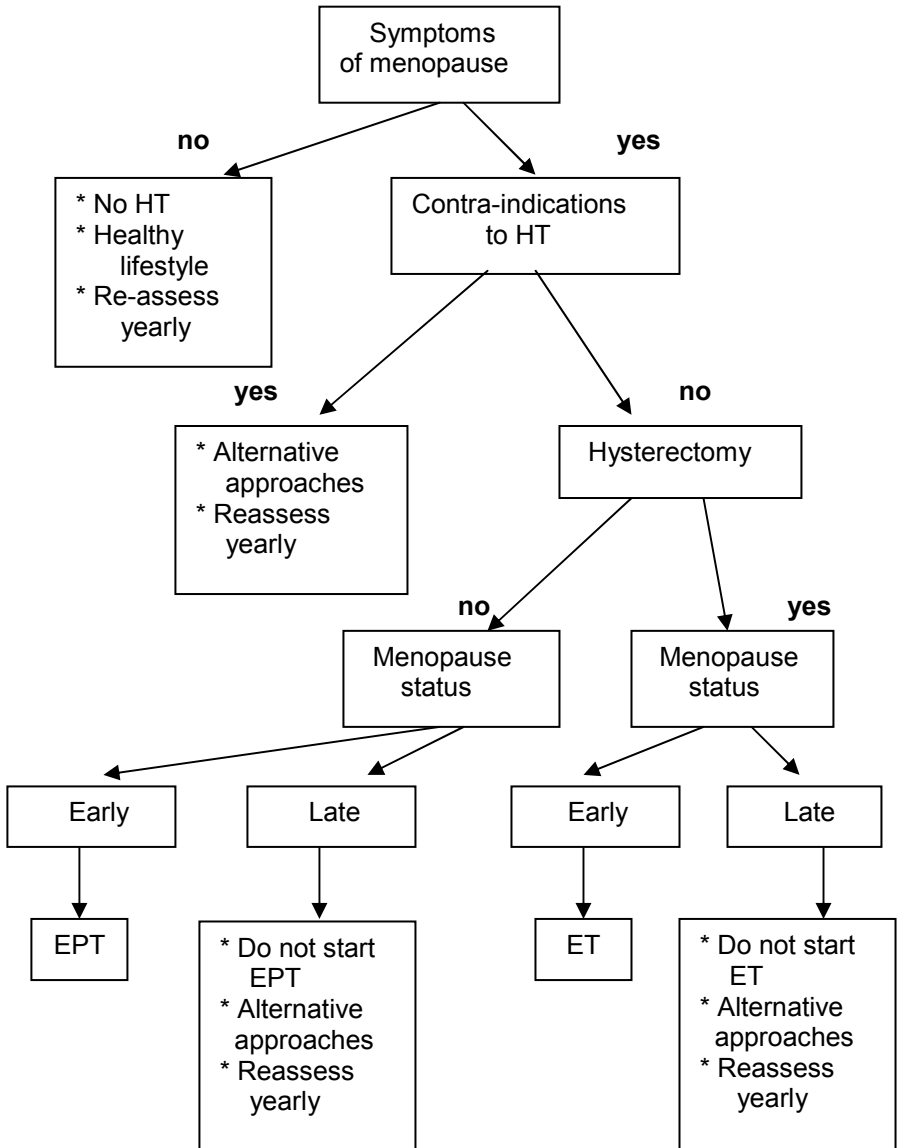
### **Hormone Therapy preparations available in Malaysia**

as on August 31, 2009

<b>Angeliq</b>		estradiol hemihydrate	1.0mg
		+ drospirinone	2.0mg
<b>Climen</b>			
	16 pills	estradiol valerate	2.0mg
	12 pills	estradiol valerate	2.0mg
		+ cyproterone acetate	1.0mg
<b>Divigel gel</b>			
	28 sachets	estradiol	1mg/g
<b>Femoston</b>			
2/10	14 pills	estradiol	2.0mg
	14 pills	estradiol	2.0mg
		+ dydrogesterone	10.0mg
1/10	14 pills	estradiol	1.0mg
	14 pills	estradiol	1.0mg
		+ dydrogesterone	10.0mg
<b>Femoston Contii</b>		estradiol	1.0mg
		+ dydrogesterone	5.0mg
<b>Oestrogel gel</b>		17 $\beta$ estradiol	1.5mg/2.5g gel
<b>Premarin</b>		conjugated equine estrogen	0.3mg, 0.625mg
<b>Premarin Vaginal Cream</b>		conjugated equine estrogen	0.3mg/0.625mg/42.5g

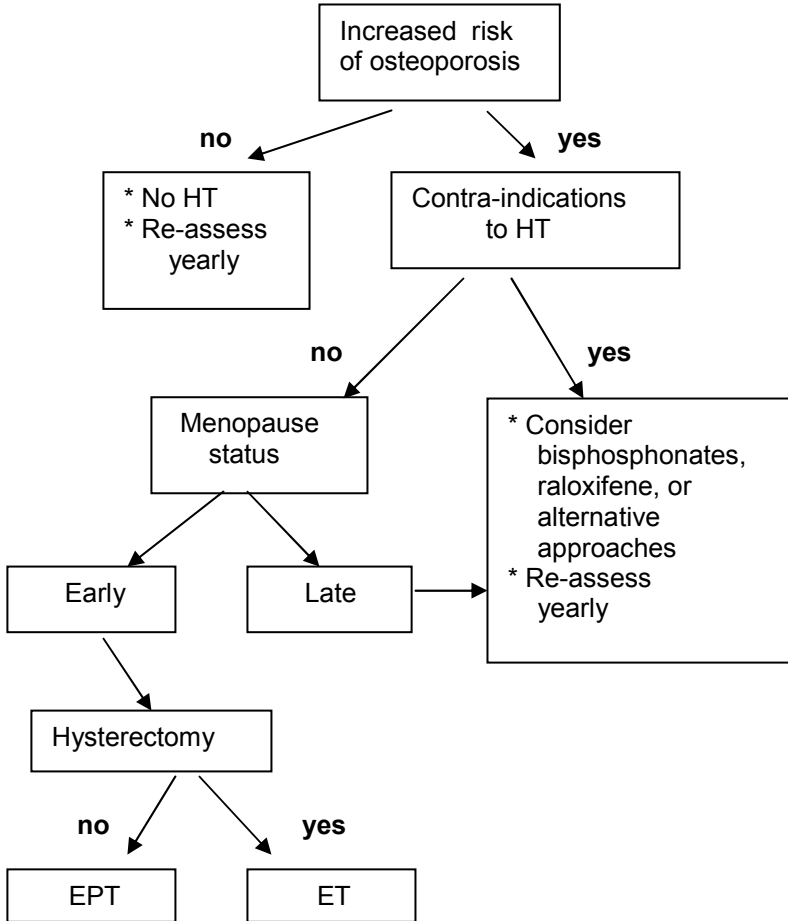
<b>Premelle 2.5</b>	conjugated equine estrogen	0.625mg
	+ medroxyprogesterone acetate	2.5mg
<b>Premelle 5.0</b>	conjugated equine estrogen	0.625mg
	+ medroxyprogesterone acetate	5.0mg
<b>Progynova</b>	estradiol valerate	1.0mg
	or	
	estradiol valerate	2.0mg
<b>Progyluton</b>		
11 pills	estradiol valerate	2.0mg
10 pills	estradiol valerate	2.0mg
	+ norgestrel	500mcg

**ALGORITHM**  
**for the initiation of HT in postmenopausal women**  
**( based on symptoms )**



APPENDIX IV

**ALGORITHM**  
**for the initiation of HT in postmenopausal women**  
**( based on risk for osteoporosis )**



## XIV. REFERENCES

**NB** Levels of evidence for the following references follow the SIGN50 criteria, revised edition 2008.

Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developer's Handbook. Annexe A. AGREE ( Appraisal of Guidelines for Research and Evaluation in Europe ) Appraisal Criteria, 2004.

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( Ref 82, APPENDIX I )

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