



CLINICAL PRACTICE GUIDELINES

Hormone Replacement Therapy



Ministry
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Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

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Hormone Replacement Therapy

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Hormone replacement therapy has the potential to be used by a great number of people. It is important that we prescribe it under the right circumstances to the right group of women who can benefit from it. As with all medication, the benefit of using the therapy must outweigh the harm.

These guidelines recommend the appropriate use of hormone replacement therapy in the treatment of menopausal symptoms and premature menopause. The guidelines also discuss the implications of the Women's Health Initiative study (WHI), a large randomised controlled trial, on the role of hormone replacement therapy in stroke, cardiovascular disease and various cancers.

I hope you find these guidelines of use to you in your practice.

DR LING SING LIN
ACTING DIRECTOR OF MEDICAL SERVICES

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Executive Summary of Recommendations

Details of recommendations can be found in the main text at the pages indicated.

A Hormone replacement therapy is recommended for the short-term control of vasomotor symptoms, vaginal dryness and urinary symptoms in menopause. (pg 10)

Grade A, Level Ib

C Combination hormone replacement therapy should not be used to reduce the risk of osteoporosis and subsequent fractures if it is the only indication for starting hormone replacement therapy. Alternatives such as bisphosphonates and raloxifene should instead be considered. (pg 10)

Grade C, Level IV

A Hormone replacement therapy should not be used for primary or secondary prevention of heart disease. (pg 10)

Grade A, Level Ib

C Prevention of colorectal cancer should not be the reason for long-term hormone replacement therapy. (pg 11)

Grade C, Level IV

A Hormone replacement therapy is not recommended for the prevention of Alzheimer's disease or dementia. (pg 11)

Grade A, Level Ib

A The use of unopposed hormone replacement therapy in a woman with an intact uterus has been shown to increase the risk of endometrial cancer by several fold. Therefore combined hormone replacement therapy should be used in patients with intact uteri. (pg 13)

Grade A, Level Ia

C Hormone replacement therapy is the cornerstone in the management of patients with premature menopause. It is effective in the relief of menopausal symptoms and protects against the long-term risks associated with prolonged estrogen deficiency. (pg 14)

Grade C, Level IV

1 Guidelines Development and Objectives

1.1 Introduction

Hormone replacement therapy (HRT) is one of the most commonly prescribed drug regimens for postmenopausal women in the world. HRT is used primarily to treat symptoms of menopause, but observational data on its beneficial effects on conditions such as osteoporosis, coronary heart disease, Alzheimer's disease and colorectal cancer has also led many women to use HRT in the hope of reducing the risks of these conditions. Recent prospective randomised controlled studies (in particular, reports arising from the Women's Health Initiative randomised controlled trial) have changed our understanding of the benefits and risks of HRT. Hence it is timely that these guidelines help to clarify the appropriate role of hormone replacement in the management of the postmenopausal woman.

1.2 WHI - What Is It's Implications On Postmenopausal Management?

WHI, the Women's Health Initiative study¹, is a 15-year multi-million dollar health endeavour established by the US National Institutes of Health (NIH) in 1991 to address cardiovascular disease, cancer and osteoporosis in postmenopausal women. One of the major components is a randomised controlled study on HRT on the prevention of major degenerative diseases. This is the largest randomised controlled trial on one combination of hormone replacement treatment. Conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg was compared against placebo in 16,608 healthy postmenopausal women aged between 50 to 79 years (average age of 63 years) with an intact uterus from 40 North American centres over a planned 8.5 years.

This particular component of the WHI study was stopped on 31 May 2002, after a mean of 5.2 years of follow-up, by the data and safety monitoring board, due to an increased risk of invasive breast cancer. Further analysis revealed that there were increased health risks of cardiovascular disease, strokes, pulmonary embolism in addition to invasive breast cancer (7/10,000 cardiovascular disease; 8/10,000 strokes; 8/10,000 pulmonary embolism; 8/10,000 breast cancer). There were reduction of risks of endometrial cancer, hip fractures and

colorectal cancers (5/10,000 hip fractures; 6/10,000 colorectal cancers). There was no increase in deaths. However, overall health risks exceeded benefits from use of this combined estrogen-progestogen therapy. It is concluded that this regimen should not be initiated for primary prevention of coronary heart disease.

Rates of dementia including Alzheimer's disease was found to be doubled in the Women's Health Initiative Memory Study (WHIMS)^{2,3} amongst 4,500 women 65 years and older in May 2003. The study also found that this regimen did not protect against the development of mild cognitive impairment.

The quality of life issues amongst the women in the WHI were also analysed and there were no significant effects on their general health, vitality, mental health, depressive symptoms or sexual satisfaction. At one year, there was a small but insignificant improvement in sleep disturbance, physical functioning and bodily pain but at three years there were no more significant benefits. However the WHI study did not include women in the early postmenopausal period or those who were symptomatic and their quality of life issues were not studied in the WHI.

The WHI study arm of conjugated estrogens on 11,000 hysterectomized postmenopausal women was stopped on 1 March 2004 by the National Institutes of Health (NIH) after about 7 years of follow-up. The current results showed that estrogen alone did not affect (either decrease or increase) the risk of coronary heart disease. At the same time, estrogen alone appears to marginally increase the risk of stroke and decrease the risk of hip fracture. The risk of breast cancer was not increased during the time period of this study. The results with estrogen alone replacement indicated that the increased risk of stroke is similar to that found in the trial of Estrogen plus Progestin when it was stopped after 5.2 years of follow up. With an average of nearly 7 years of follow-up completed, the study results are not likely to change if the trial continues for one more year. Thus, the NIH believes that enough data have been obtained to provide an overall assessment of the risks and benefits of the use of estrogen in this trial.

Overall the combination regime of estrogen-progestogen does not seem to be beneficial in the prevention of coronary heart disease, strokes or cognitive function especially in the older postmenopausal woman. The increase in risk of invasive breast cancer albeit small in these women over time will always limit the use of HRT in the long term, despite the positive benefits of HRT on osteoporosis and colorectal cancer. It does seem that the combined regime of HRT is probably only suitable for the early menopausal woman suffering from significant menopausal symptoms.

Although the trial was on one particular combination of hormone replacement, the findings of WHI has a potential of being extrapolated to other estrogen and progestogen preparations and has deeply affected prescriptions of hormone therapy throughout the world.

1.3 Objectives

These guidelines aim to address the following issues:

- Indications for the use of hormone replacement therapy in the healthy postmenopausal woman
- Safety issues in the use of hormone replacement therapy
- Principles of treatment, dosing and optimal duration of therapy
- Treatment of premature menopause
- Answers to frequently asked questions about hormone replacement therapy

1.4 Guidelines Development

These guidelines were developed by a workgroup made up of specialists in the field of obstetrics and gynaecology with a special interest in hormone replacement therapy and care of menopausal woman, as well as a family practitioner. An exhaustive search into the medical literature as well as guidelines from various colleges around the world formed the basis of these guidelines and recommendations.

1.5 Target Group

Menopausal women form a large group of women patients seen by both specialists and the general practitioner. It is envisaged that these guidelines will provide a framework to update practitioners in the indications for HRT.

1.6 Review of Guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review three years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Definition of Menopause and Treatment of Menopausal Symptoms

2.1 Definition

Menopause is defined as the end of a woman's reproductive lifespan and is achieved one year after the last period. The median age of menopause in women in Singapore is 49 years. However, the ovarian production of estrogen and progesterone begins to decline years before the complete cessation of menses and therefore menopausal symptoms start even before the cessation of menstrual periods.

Menopausal symptoms include the following:

- Vasomotor symptoms of hot flushes and night sweats
- Vaginal dryness
- Urinary frequency, urgency and stress incontinence
- Reduced libido
- Mood swings
- Insomnia

2.2 Dosing and Routes of Administration of Hormone Replacement Therapy

Estrogen-only replacement therapy may be offered to women who have had hysterectomies. In women with intact uteri, estrogen should be offered with progestogen, to protect the endometrium. These may be given in a cyclical fashion, which results in regular withdrawal bleeding, or in a continuous fashion, where there is no vaginal bleeding.

Hormone replacement therapy is indicated in the patient with climacteric symptoms and the dose for the treatment should be the lowest needed for the control of symptoms and the duration of therapy should also be the shortest possible. In general 6 to 12 month period may be envisaged. However, longer periods may be necessary for more persistent symptoms. Generally menopausal symptoms will resolve within 5 years.

Systemic Treatment:Estrogens

Drug	Suggested Daily Dose
<i>Oral</i>	
Conjugated Equine Estrogen (Premarin)	0.3-0.625 mg
Estradiol (Estrafem)	1-2 mg
Estradiol Valerate (Progynova)	1-2 mg
<i>Transdermal</i>	
Estradiol patch (Estraderm)	50 µg
Estrogel	1.5 mg
Estradiol Hemihydrate (Estreva gel)	1% 50 g

Progestogens

Drug	Suggested Daily Dose
Medroxyprogesterone Acetate (Provera)	2.5, 5 or 10 mg
Dydrogesterone (Duphaston)	5, 10 or 20 mg
Norethisterone (Micronor)	2.5, 5 or 10 mg
Intrauterine L-norgestrel system (Mirena)	1 system for up to 5 years (20 ug / 24 h)
Micronised progesterone (Utrogestan)	50, 100 mg

Cyclical Combined Therapies

Oral Therapy	Daily Estrogen Dose	Progestogen Dose
Estradiol valerate and norgestrel (Progylluton)	2 mg	0.5 mg for 10 days 21 day cycle
Estradiol valerate and cyproterone acetate (Climens)	2 mg	1 mg for 10 days 21 day cycle
Conjugated equine estrogen and norgestrel (Prempak-C)	0.625 mg	0.15 mg for 12 day 28 day cycle
Conjugated equine estrogen and medroxyprogesterone acetate (Premelle cycle 5)	0.625 mg	5 mg for 14 days 28 day cycle
Estradiol and dydrogesterone (Femoston)	2 mg	10 mg for 14 days 28 day cycle
Estradiol and norethisterone acetate (Trisequens)	2 mg for 22 days 1 mg for 6 days	1 mg for 10 days 28 day cycle

Continuous Combined Therapies

Combined therapy	Daily estrogen dose	Progestogen dose
Conjugated equine estrogen and medroxyprogesterone acetate (Premelle 5 or Premelle 2.5)	0.625 mg	5 mg 2.5 mg
Estradiol and norethisterone acetate (Kliogest or Activelle)	2 mg 1 mg	1 mg 0.5 mg

Local Therapy

Those with symptoms isolated to the urogenital tract should consider the use of topical estrogen therapy. With the exception of Premarin cream, there is minimal systemic absorption of the estrogen and therefore local estrogen therapy is not associated with the adverse effects seen with systemic estrogen

replacement therapy. There is also little effect on the endometrium and therefore progestogens do not have to be added. Treatment for prolonged periods may require monitoring on the effects on the endometrium.

Drug	Dosage
Estradiol pessary (Vagifem)	25 µg daily for two weeks followed by 25 µg twice a week
Conjugated equine estrogen cream (Premarin cream)*	1 g daily
Colpotrophine 1% cream	1 to 2 cm
Colpotrophine pessary 10%	1 daily up to 20 days
Estradiol ring (Estring)	2 mg estradiol vaginal ring every 90 days

* Premarin cream – when used for vaginal atrophy should have progestogen coverage if used longer than 3 months.

Livial®⁴ contains tibolone - a selective tissue estrogenic activity regulator (STEAR) - which regulates estrogenic activity in a tissue selective way. These tissue-selective properties of Livial enable it to provide effective relief of climacteric symptoms and vaginal atrophy, enhance mood and sexual well being and prevent osteoporosis. In the endometrium and breast tissue, it does not stimulate proliferation. The present guidelines do not include Livial as it is not an estrogen nor progestogen.

Phytoestrogens are weak estrogens found in plants and their role in the treatment of menopausal management is not substantiated with good peer-reviewed studies. They are not included in these guidelines.

2.3 Hormone replacement therapy is effective in the treatment of menopausal symptoms

Hormone replacement therapy is effective in the treatment of vasomotor symptoms, vaginal dryness and the treatment of urinary symptoms, especially with surgery with some improvement in stress incontinence. Hormone replacement therapy is effective in improving

the quality of life, especially in the subgroup with vasomotor symptoms.⁵⁻⁸

A Hormone replacement therapy is recommended for the short-term control of vasomotor symptoms, vaginal dryness and urinary symptoms in menopause.

Grade A, Level Ib

2.4 Role of Hormone Replacement Therapy and Osteoporosis

Hormone replacement therapy reduces the risk for hip fractures.⁵ However, combination HRT should not be used solely for this purpose due to its possible longer term adverse effects.

C Combination hormone replacement therapy should not be used to reduce the risk of osteoporosis and subsequent fractures if it is the only indication for starting hormone replacement therapy. Alternatives such as bisphosphonates⁹ and raloxifene¹⁰ should instead be considered.

Grade C, Level IV

2.5 Role of Hormone Replacement Therapy and Heart Disease

Current evidence does not demonstrate any benefit in the use of estrogen replacement therapy¹¹ or combination hormone replacement therapy¹² for reduction of coronary heart disease, whether as a secondary prevention^{13,14} measure for women at high risk of the disease, or as a primary prevention measure for women at low risk of the disease.

A Hormone replacement therapy should not be used for primary or secondary prevention of heart disease.

Grade A, Level Ib

2.6 Role of Hormone Replacement Therapy in the Prevention of Colorectal Cancer

Hormone replacement therapy reduces the incidence of colorectal cancer.⁵ However, combination HRT should not be used solely for this purpose due to its possible longer term adverse effects.

C Prevention of colorectal cancer should not be the reason for long-term hormone replacement therapy.

Grade C, Level IV

2.7 Role of Hormone Replacement Therapy in the Prevention of Dementia

There is no evidence to suggest that the use of combined hormone replacement therapy improves cognition² or protects against dementia.³

A Hormone replacement therapy is not recommended for the prevention of Alzheimer's disease or dementia.

Grade A, Level Ib

3 Safety Issues of Hormone Replacement Therapy

Breast tenderness, irregular vaginal bleeding and headaches are common side effects of hormone replacement. There are, in addition, other serious adverse effects.

3.1 Deep Vein Thrombosis and Pulmonary Embolism

The use of combined hormone replacement therapy is associated with a significant risk of deep vein thrombosis and pulmonary embolism.⁵

3.2 Stroke

The use of combined hormone replacement therapy is associated with a small increase in the incidence of ischaemic strokes^{1,5} in healthy postmenopausal women. In contrast, combined hormone replacement therapy did not increase the risk of hemorrhagic stroke.

3.3 Breast Cancer

The long term use of combined hormone replacement therapy and estrogen replacement therapy are associated with a small but significant risk of breast cancer.^{5,12,15} The excess risk is seen after more than 4 years of treatment.

The magnitude of this adverse effect appears to be greater among users of combined hormone replacement therapy than those on unopposed estrogen replacement therapy.^{5,12} The excess risk is seen after more than 4 years of treatment. The estrogen-only arm of the WHI study in hysterectomized women did not show an increased incidence of breast cancer.¹⁶

There is evidence that mammographic changes associated with hormone usage may hinder and delay the diagnosis of breast cancer.¹⁵

3.4 Endometrial Cancer

A The use of unopposed hormone replacement therapy in a woman with an intact uterus has been shown to increase the risk of endometrial cancer by several fold.^{17,18} Therefore combined hormone replacement therapy should be used in patients with intact uteri.

Grade A, Level Ia

Combined hormone replacement therapy, whether in cyclical regimen (with the progestin component used for > 12 days per cycle month) or in continuous regimen, has been shown to confer adequate endometrial protection and is not associated with any increased risk of endometrial cancer.^{19,20}

4 Premature Menopause

4.1 Definition

Premature menopause is defined as spontaneous menopause before the age of 40 years.²¹ The condition is characterized by primary or secondary amenorrhoea, infertility, sex steroid deficiency and elevated serum gonadotrophin levels. The consequence of premature ovarian failure is similar to those of the later 'natural' menopause. This condition is associated with premature loss of fecundity and the impact of health problems secondary to the long term deficiency such as osteoporosis. Premature menopause affects about 1% of women under the age of 40 years.²²

4.2 Management of Patients with Premature Menopause

In light of more recent studies about hormone replacement therapy, it is uncertain whether the risks associated with combined HRT usage may be extrapolated to younger women with premature menopause. In these women the benefits of treatment may far outweigh the risks.

C Hormone replacement therapy is the cornerstone in the management of patients with premature menopause. It is effective in the relief of menopausal symptoms and protects against the long-term risks associated with prolonged estrogen deficiency.⁵⁻⁸

Grade C, Level IV

5 Answers to Frequently Asked Questions

Q1: Does HRT increase the risk of cerebrovascular accidents?

Ans: Estrogen plus progestin use increases the risk of ischaemic stroke in healthy postmenopausal women.¹

Q2: Does taking HRT decrease the risk of Alzheimer's disease in postmenopausal women?

Ans: No. In older postmenopausal women, aged 65 years and above, estrogen plus progestin therapy did not improve cognitive function when compared to placebo. There were significantly more women in the estrogen plus progestin group with a substantial and clinically important cognitive decline.²

Q3: Does HRT have an effect on uterine myomas in postmenopausal women?

Ans: The effect of hormone replacement therapy on uterine fibroid size is controversial. Some studies have shown an increase in uterine size and myoma size, while other studies have shown no effect on uterine bleeding patterns.

Clinically, uterine myomas are generally not stimulated to grow by hormone replacement therapy. However, it is important to maintain vigilance and continue regular pelvic examinations.²³⁻²⁷

Q4: What is the effect of HRT on the risk of colorectal cancer?

Ans: The use of combined estrogen plus progestin therapy decreases the risk of colorectal cancer.^{28,29} However, hormone replacement therapy is not recommended for this purpose due to its possible longer term adverse effects.

Q5: Does HRT increase the risk of venous thromboembolism?

Ans: The use of combined postmenopausal estrogen plus progestin treatment increases the risk for venous thrombosis and pulmonary embolism.^{28,30}

Q6: Does HRT increase the risk of carcinoma of the endometrium?

Ans: No. If a woman with an intact uterus receives a preparation containing a combination of an estrogen and 12 days of progestogen, there is no increase in the risk of endometrial cancer.^{20,28,31-33}

Q7: Does HRT increase the risk of carcinoma of the ovary?

Ans: There is no increased risk of carcinoma of the ovary in users of postmenopausal estrogen plus progestin replacement therapy.

There may be an increased risk of ovarian cancer in women who use unopposed estrogen for a long time and the magnitude of risk noted is low.^{28,34,35}

Q8: Can HRT increase the risk of recurrence of endometriosis after surgery?

Ans: The common denominator for endometriosis formation appears to be exposure to female hormones.

In girls with gonadal dysgenesis, there have been case reports describing endometriosis development after initiation of estrogen therapy.

There are even case reports of men developing endometriosis after receiving high doses of estrogen therapy for bladder or prostate cancer.

It has been shown that a minority of women develop a recurrence of endometriosis after radical surgery related to the commencement of hormone replacement therapy.

There are also case reports of endometriosis arising de novo following hormone replacement therapy.

Case reports have suggested that the use of unopposed estrogen may lead to premalignant or malignant transformation in residual foci of endometriosis.³⁶⁻⁴⁷

Q9: Does HRT usage worsen the blood pressure in hypertensive women?

Ans: No. Estrogens at the doses used for postmenopausal HRT have been found to either have no effect on blood pressure or to cause a small but statistically significant decrease.⁴⁸⁻⁵¹

6 Clinical Audit Parameters

The following clinical audit parameter is proposed:

- Percentage of women with intact uteri on hormone replacement therapy receiving estrogen-only therapy.

The use of unopposed hormone replacement therapy in a woman with an intact uterus has been shown to increase the risk of endometrial cancer by several fold.^{17,18} Therefore combined hormone replacement therapy should be used in patients with intact uteri.

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Self-assessment

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this assessment. This is an extension of the learning process and is not intended to “judge” your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose the right answer.

1. Combined estrogen-progestin replacement therapy increases the risk of endometrial cancer.
A. True B. False
2. Hormone replacement therapy is indicated in diabetic patients with hypercholesterolaemia to reduce the risk of coronary artery disease.
A. True B. False
3. In a woman presenting with menopausal symptoms of hot flushes and vaginal dryness, but with a family of breast cancer, should be treated with raloxifene instead of estrogen replacement therapy.
A. True B. False
4. Local vaginal estrogen replacement should be used together with progestins in women with an intact uterus.
A. True B. False
5. Premature menopause is associated with significant health implications and hormone replacement therapy should be considered.
A. True B. False

6. A history of breast cancer is a definite contraindication to the usage of hormone replacement therapy.

A. True B. False

7. Oral estrogen replacement therapy is more effective than topical vaginal estrogens in the treatment of urogenital symptoms associated with menopause.

A. True B. False

8. Estrogen replacement alone when used in a post-hysterectomy patient is not associated with an increased risk of breast cancer.

A. True B. False

Answers:

1. False
2. False
3. False
4. False
5. True
6. True
7. False
8. True

Workgroup Members

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