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Guidelines for the Administration of Hormone Replacement Therapy

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1 INTRODUCTION

HRT may be offered to postmenopausal or symptomatic perimenopausal women, and their decision to use it will rest upon the balance between the advantages and disadvantages of treatment

1.1 Menopausal symptoms

Oestrogen is effective in reducing the severity and frequency of hot flushes and sweating. There is less evidence to show that oestrogen is effective in controlling other acute symptoms attributable to the menopause[1]. Whilst some Chinese women suffer from severe vasomotor symptoms, these occur less commonly than in Caucasians[2,3]. Menopausal symptoms may therefore be a relatively less important indication for treatment in Chinese women.

1.2 Prevention and treatment of Osteoporosis

Bone loss after the menopause especially affects the femoral neck and lumbar spine. The administration of oestrogen with or without a progestogen is effective in preventing bone loss in these sites[4]. In the recent Womens Health Initiative trial[5], predominantly healthy women were randomised to receive either conjugated equine oestrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg daily or placebo for an average of just over 5 years. This part of the study was terminated prematurely as there was an increase in the risk of breast cancer and cardiovascular disease that appeared to outweigh the beneficial effect of treatment on fracture prevention and a reduction in risk of cancer of the colon. However, it confirmed that this treatment protected against both vertebral and hip fracture. The risk of vertebral fracture was 9/10,000 person years in the treatment group and 15/10,000 person years in the placebo group. For hip fracture, the risk was 10/10,000 person years in the treatment group compared with 15/10,000 person years in the placebo group.

Bone mineral density (BMD) studies can be useful in decision making regarding the use of HRT. BMD studies should especially be considered for those women with risk factors for osteoporosis (Appendix 1). As far as osteoporosis is concerned, once oestrogen treatment is discontinued, protection against bone loss is largely lost.

For women who are already osteoporotic, treatment with the bisphosphonates alendronic acid and risedronic acid, or with the selective estrogen receptor modulator (SERM) raloxifene has been shown to reduce the incidence of vertebral fractures. The bisphosphonates have also been shown to reduce the risk of non-vertebral fractures[6].

1.3 Prevention against Cardiovascular Disease

Epidemiological evidence suggests that the administration of oestrogen reduces cardiovascular risk in healthy postmenopausal women[7]. The beneficial actions of oestrogen include an improvement in the lipid profile, a reduction in cholesterol uptake by the vessel wall and an increase in blood flow due to arterial relaxation. Oestrogen is also thought to act as an antioxidant and a calcium antagonist, and it also increases insulin sensitivity. As stated above, in the Womens Health Initiative trial[5], it was found that cardiovascular risk was higher in the users of conjugated equine oestrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg than in the placebo group. These data may or may not apply to the use of oestrogen alone. The arm of the WHI trial in which oestrogen alone is being used is ongoing. In the WHI trial, the risk of a cardiovascular event was 37/10,000 person years in the treatment group and 30/10,000 person years in the placebo group. There were also significant increases in risk of stroke and venous thromboembolism in the treatment groups compared with placebo.

It is now agreed that HRT should not be started in women with established heart disease, as this may precipitate a cardiac event[8]. In addition, combined HRT should not be used solely for the purpose of primary prevention of cardiovascular disease. It is still uncertain whether the use of oestrogen alone is beneficial for the cardiovascular system. Also, it is not known whether combinations of HRT other than those used in the WHI trial have a different effect on cardiovascular risk.

1.4 Improvement in Quality of Life

The use of HRT improves cognition in women who are symptomatic of the menopause. Specific improvements have been shown in verbal memory, vigilance, reasoning and motor speed. HRT may also decrease the risk of dementia[9].

1.5 Reduction in risk of colon cancer

A recent meta-analysis showed a significant reduction in the risk of colon cancer in ever users of HRT[10]. The WHI trial also showed that combined HRT reduced the risk of cancer of the colon. The risk of carcinoma of the colon was 10/10,000 person years in the treatment group compared with 16/10,000 person years in the placebo group.

2 DISADVANTAGES AND RISKS OF HRT

The risks and benefits of HRT have in part been discussed above. In addition, for some women who have not had a hysterectomy, the resumption of menstrual-like bleeding may be considered to be a disadvantage of treatment.

The most serious risk attributed to the use of HRT is that of breast cancer. Many studies have been performed which suggest that the administration of HRT does not increase the risk of breast cancer, whilst others have suggested a slight increase in risk[11]. In studies that have identified an increased risk, this does not appear to become significant until after 5 years of use of HRT[12]. In the WHI trial, the risk of breast cancer was 38/10,000 person years in the treatment group and 30/10,000 person years in the placebo group.

An increased risk of breast cancer should probably not be an issue for short term users of HRT.

The most common side effects of HRT are breast sensitivity or engorgement and fluid retention. These problems tend to improve within months of initiating treatment, but if necessary the dose of oestrogen may be reduced to a level of comfort.

2.1 Absolute contraindications to the use of HRT

Existing breast carcinoma
Existing endometrial carcinoma
Venous thrombosis
Acute liver disease

3 PRESCRIPTION OF HORMONE REPLACEMENT THERAPY

For the purpose of hormone replacement, oestrogen may be administered orally, percutaneously, transdermally, in a subcutaneous implant or intranasally. For safety, the lowest possible dose should be used. The doses listed at the end of this document are usually the maximum dose needed. Many women feel better on lower doses than those listed, and it is better for a patient to stay on a lower dose than to stop altogether because of side effects from a higher dose.

Regarding mode of delivery, vaginal administration of oestrogen is usually reserved for the short term treatment of lower genital tract symptoms. For most women, the route of administration of oestrogen can be chosen according to their preference. Those with medical conditions which can in theory be affected by the hepatic "first pass" effect of oral oestrogens may be better treated with non-oral preparations. This includes women with diabetes mellitus, hypertension and hypertriglyceridaemia.

3.1 Unopposed oestrogen

Unopposed oestrogen implies the use of oestrogen without a progestogen. In those women who have had a hysterectomy, unopposed oestrogen should be prescribed. For those women who still have a uterus, a progestogen should be given in addition to oestrogen to prevent endometrial hyperplasia and carcinoma[13]. The prescription of oestrogen as well as a progestogen is referred to as combined HRT, and this combination may be given either cyclically (sequentially) or continuously (see below).

3.2 Combined cyclical (sequential) HRT

A cyclical (sequential) regimen implies that a progestogen is given on a cyclical basis (in addition to oestrogen), and this cyclical use of a progestogen usually results in regular withdrawal bleeding at the end of each progestogen cycle. When prescribing HRT at the time of (or soon after) the menopause, a cyclical (sequential) regimen is less likely to cause irregular bleeding than would a continuous combined regimen (see Section 3.3). With a cyclical regimen, oestrogen is usually prescribed for 21 or 28 days whilst the progestogen is given for 10 or 12 days each month. A small percentage of women may become amenorrhoeic during cyclical treatment.

3.3 Continuous combined HRT

For women with an established menopause (≥ 2 years), continuous combined HRT can be given, in which case both the oestrogen and a progestogen are given on a daily basis. On such a regimen, the aim is for these women to remain amenorrhoeic. Spotting is common during the first few months of this treatment.

An alternative to continuous combined HRT is the use of tibolone, a synthetic agent which has weak oestrogenic, androgenic and progestogenic properties. This drug can be used under the same circumstances as continuous combined oestrogen and a progestogen.

3.4

Recent data on a new class of drugs referred to as selective estrogen receptor modulators suggests that these preparations reduce the risk of breast and endometrial cancer[14,15]. They have a beneficial effect on lipids and bone, but little or no therapeutic effect on acute menopausal symptoms. In fact, in some cases, they can induce hot flushes in women who were previously asymptomatic. One of these, raloxifene, is FDA approved for the treatment of osteoporosis. These drugs may be desirable for asymptomatic women with a fear of breast cancer who wish to prevent osteoporosis or those with risk factor(s) for breast cancer. The SERMs may be prescribed for women with or without a uterus.

3.5 Duration of use of HRT

There are no rules regarding the duration of use of HRT. The results of the WHI study suggest that caution should be used when prescribing HRT in the long term.

4 MANAGEMENT OF THE MENOPAUSE

Treatment can begin at any time after the menopause, and the type of HRT regimen will be dictated by the duration of the menopause and whether or not a hysterectomy has been performed. Women may start treatment before the menopause, at the time of menopause, years after the menopause or not at all. There is no fixed minimum or maximum duration of treatment.

Some women develop symptoms of oestrogen deficiency before the menopause occurs, and treatment may begin at this time although irregular bleeding after the start of treatment in perimenopausal women may be a problem.

Apart from the use of HRT, attention to life style factors which promote good health should be encouraged. These include weight control and regular weight bearing exercise.

4.1 Monitoring of women using HRT

Cervical smears should be performed routinely as for all women with a uterus. Compliance with treatment, symptom control, side effects (if any) and the bleeding pattern of those on combined treatment should be noted at each visit. In addition, women should be encouraged to be "breast aware", i.e. alert to any changes in their breasts.

The following examinations and investigations are commonly performed, but there is no universal agreement as to which of these are essential. Mammograms should be interpreted with caution because the sensitivity of mammography in detecting breast cancer appears to be slightly lower in users than in non-users[16]:

4.1.1 At first visit:

FSH/LH/E_2 to confirm menopause (if clinical features atypical)
Lipid profile/Liver function tests/Bone biochemistry/TSH
Mammography

4.1.2. At each visit:

Urinalysis
Blood pressure

4.1.3. Every two years:

Physical examination
Lipid profile/Liver function tests
Fasting glucose
Mammography

4.1.4 As indicated:

Bone mineral density studies

4.2 Management of irregular bleeding on HRT

4.2.1 Women using combined cyclical HRT

Some women will be amenorrhoeic on this regimen, and a biopsy is not necessary. Bleeding should occur around the time of progestogen withdrawal. If bleeding occurs at times other than this or is persistently irregular, endometrial biopsy is recommended.

4.2.2 Women using continuous combined HRT

Ideally women using continuous combined HRT should achieve amenorrhoea within about 4 months of starting treatment. Spotting in the first few months is common. Endometrial biopsy should be considered in women who were previously amenorrhoeic but who subsequently develop irregular bleeding.

5 EXAMPLES OF PREPARATIONS AVAILABLE IN HK AND DOSES (AS OF MAY 2002)

5.1 Unopposed oestrogen

	Generic	Trade
Oral	Conjugated oestrogens 0.625mg daily	PREMARIN, CONJUGATED OESTROGENS JEAN-MARIE
Oral	Oestradiol 2mg daily	ESTROFEM
Oral	Oestradiol valerate 2mg daily	PROGYNOVA
Oral	Oestriol 0.27 mg, oestradiol 0.6 mg, oestrone 1.4 mg	HORMONIN
Oral	Oestriol 1 mg	OVESTIN
Gel	Percutaneous oestradiol gel 2.5g daily	OESTROGEL
Gel	Percutaneous oestradiol gel 1.5 g daily	ESTREVA
Patch	Oestradiol 4mg patches (2 patches/week)	DERMESTRIL or ESTRODERM TTS
Intranasal	Oestradiol 150 mcg/spray	AERODIOL

5.2 Combined cyclical (sequential)

	Generic	Trade
Oral	Oestradiol 2mg daily + dydrogesterone 10mg 14/28 days	FEMOSTON
Oral	Oestradiol 2mg 22 days/1mg 6 days + norethisterone acetate 1mg daily 10/28 days	TRISEQUENS
Oral	Oestradiol valerate 2mg daily + cyproterone acetate 1mg 12/28 days	CLIMEN 28
Oral	Conjugated equine oestrogens 0.625mg daily + medroxyprogesterone acetate 5mg 14/28 days	PREMELLE CYCLE
Oral	Oestradiol valerate 2mg daily + Medroxyprogesterone acetate 10 mg 10/21 days	DILENA
Oral	Oestradiol valerate 2 mg + levonorgestrel 0.15 mg 12/21 days	KLIMONORM
Patch	Oestradiol 4mg patches (2 patches/week) for 2/52 followed by oestradiol 10mg + norethisterone acetate 30mg patches (2 patches/week) for 2/52	ESTROCOMB TTS

5.3 Continuous combined

	Generic	Trade
Oral	Conjugated equine oestrogens 0.625 mg + medroxyprogesterone acetate 2.5mg daily	PREMELLE
Oral	Oestradiol 2 mg + norethisterone acetate 1mg daily	KLIOGEST
Oral	Oestradiol 1 mg + norethisterone acetate 0.5 mg daily	ACTIVELLE
Oral	Tibolone 2.5 mg daily	LIVIAL

5.4 Selective Estrogen Receptor Modulators

	Generic	Trade
Oral	Raloxifene 60 mg daily	EVISTA

APPENDIX:

Appendix 1. Risk factors for osteoporosis

1. Prolonged oligomenorrhoea/amenorrhoea or a premature menopause

2. Prolonged immobilization/inactivity

3. Excessive intake of alcohol or caffeine; smoking

4. Those with low BMI, short stature, family history

5. Those taking drugs which predispose to osteoporosis e.g. steroids, thyroxine, anticonvulsants

6. Medical conditions which predispose to osteoporosis
   - Cushing's Syndrome
   - Hyperthyroidism
   - Hyperparathyroidism
   - Chronic diseases - liver or kidney
   - Malabsorptive disorders
   - Gastrectomy
   - Rheumatoid arthritis

REFERENCES:

1. Hunter MS. The effects of estrogen on mood and well-being. In: The Modern Management of the Menopause; A perspective for the 21st century. Berg G, Hammar M (eds). Parthenon Publishing, UK. 1994:177-184

2. Haines CJ, Chung TKH, Leung DHY. A prospective study of the frequency of acute menopausal symptoms in Hong Kong Chinese women. Maturitas 1994;18:175-181

3. Tang GWK. Menopausal symptoms. J Hong Kong Med Assoc 1993;45:249-254

4. Lindsay R. The role of estrogen in the prevention of osteoporosis. Endocrinol Metabol Clin North Am 1998; 27:399-409

5. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy women. JAMA 2002;288:321-332

6. Hochberg M. Preventing fractures in postmenopausal women with osteoporosis: a review of recent controlled trials of antiresorptive agents. Drugs & Aging 2000;17:317-330

7. Beale CM, Collins P. The menopause and the cardiovascular system. Baillieres Clin Obstet Gynaecol 1996;10:483-513

8. Hully S, Grady D, Bush TL, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613

9. LeBlanc ES, Janowsky J, Chan BKS et al. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001;285:1489-1499

10. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106:574-582

11. Burger CW. Kenemans P. Postmenopausal hormone replacement therapy and cancer of the female genital tract and breast. Current Opinion in Obstetrics & Gynecology 1998; 10:41-5

12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and HRT: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-1059)

13. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Pettiti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995;85:304-14

14. Baynes KCR, Compston JE. Selective oestrogen receptor modulators: a new paradigm for HRT. Current Opinion in Obstetrics & Gynecology 1998;10:189-9214

15. Cauley JA, Norton L, Lippmen ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Breast Cancer Research and Treatment 2001;65:125-134

16. Kavanagh AM, Mitchell H, Giles CG. HRT and accuracy of mammographic screening. Lancet 2000;355: 270-274

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This guideline was produced by The Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practising in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognised clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.

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An algorithm for the administration of HRT