Guidelines for the administration of hormone replacement therapy. The Hong Kong College of Obstetricians and Gynaecologists

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Objective. To establish guidelines on the administration of hormone replacement therapy in Hong Kong for a primary audience of Fellows and Members of the Hong Kong College of Obstetricians and Gynaecologists and a secondary audience of all interested medical and paramedical personnel in Hong Kong.
Participants. The Quality Assurance Committee established a consensus panel of four College Fellows who had expertise of treating menopausal women by giving hormone replacement therapy. All the panelists were qualified obstetricians and gynaecologists.
Evidence. The panelists drew their conclusions from the available scientific literature on hormone replacement therapy from Hong Kong and overseas.
Consensus process. The consensus reached within the panel was presented to the Quality Assurance Committee on 23 June 1998, and subsequently revised and presented three times. The final version was approved by the Quality Assurance Committee on 2 March 1999 and the Council of the Hong Kong College of Obstetrics and Gynaecology on 11 March 1999.
Conclusions. The administration of hormone replacement therapy is effective in reducing the severity and frequency of menopausal hot flushes and sweating. Therapy protects against osteoporosis and reduces the risk of cardiovascular disease. There is some evidence to suggest that treatment also protects against Alzheimer's disease and carcinoma of the colon. The most serious problem attributed to using hormone replacement therapy is the possible increase in the risk of breast cancer development; the exact risk is unknown. Side effects include unwanted bleeding and breast tenderness and sensitivity. The risks and benefits of using hormone replacement therapy should be explained to postmenopausal women so that they can make an informed decision about using this treatment.

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(1) Benefits of hormone replacement therapy

The benefits of hormone replacement therapy (HRT) are the following:
(a) Relief of menopausal symptoms
(b) Prevention of osteoporosis
(c) Prevention of cardiovascular disease

The administration of HRT may also reduce the risk of Alzheimer's disease, but there are fewer supporting data.[1]

Hormone replacement therapy may be offered to most postmenopausal or symptomatic perimenopausal women, and their decision to use HRT will depend on the balance between the advantages and disadvantages of treatment that are explained to them.

(1.1) Menopausal symptoms

Oestrogen is effective in reducing the severity and

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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.[2] While severe vasomotor symptoms develop in some Chinese menopausal women, these symptoms occur less commonly than they do in Caucasians.[3,4] Severe vasomotor symptoms may thus be a relatively less important indication for treatment in Chinese women.

(1.2) Prevention of osteoporosis

Bone loss after the menopause especially affects the femoral neck and lumbar spine. The administration of oestrogen is effective in preventing osteoporosis and osteoporotic fractures in these sites.[5] Bone mineral density (BMD) studies performed in Hong Kong can provide information that may be beneficial when deciding to use HRT. Studies should especially be considered for women who are at risk of osteoporosis development (Box 1 lists the risk factors). The disadvantage of determining the BMD, however, is the cost involved. As far as osteoporosis is concerned, once oestrogen treatment is discontinued, protection against bone loss is largely lost.

(1.3) Prevention of cardiovascular disease

There is indirect evidence to suggest that the administration of oestrogen reduces cardiovascular risk by as much as 50%.[6] The beneficial actions of oestrogen include an improvement in the serum 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. The cardioprotective effect of oestrogen applies to current as well as previous users of HRT. Women who are at increased risk of cardiovascular disease should especially benefit from treatment (Box 2 lists the risk factors).

Box 1. Risk factors for osteoporosis

(1) Prolonged oligomenorrhoea/amenorrhoea or premature menopause
(2) Prolonged immobilisation/inactivity
(3) Excessive intake of alcohol or caffeine; smoking
(4) Low body mass index, short stature, family history of osteoporosis
(5) Use of drugs that predispose to osteoporosis, eg steroids, thyroxine, anticonvulsants
(6) Medical conditions that predispose to osteoporosis such as:
Cushing's syndrome
hyperthyroidism
hyperparathyroidism
chronic disease of the liver or kidney
malabsorptive disorders
gastrectomy
rheumatoid arthritis

Box 2. Risk factors for cardiovascular disease

(1) Existing cardiovascular disease
(2) Family history of cardiovascular disease
(3) Hypercholesterolaemia
(4) Smoking
(5) Diabetes mellitus
(6) Hypertension
(7) Obesity

(2) Disadvantages and risks of hormone replacement therapy

The main disadvantage of HRT is the necessity to use one or other of the hormone preparations for a relatively long period of time. 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 the development of breast cancer. The extent of the risk cannot at present be accurately estimated. Many studies suggest that the administration of HRT does not increase the risks of breast cancer, while others suggest a slight increase in risk.[7] Studies are currently being performed overseas and may more accurately measure the risk.

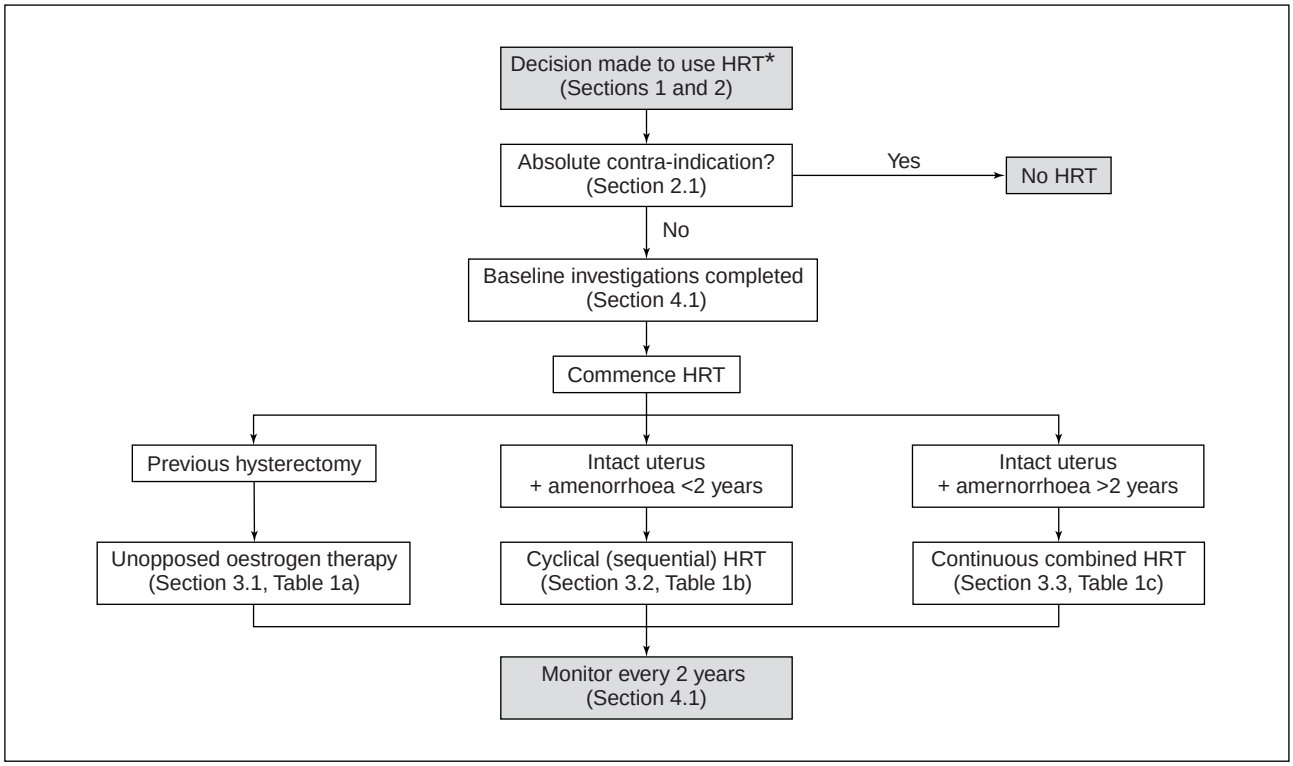
The most common side effects of HRT are breast sensitivity or engorgement and fluid retention. These problems tend to improve within months of initiating treatment, but the dose of oestrogen given may be reduced to relieve the discomfort.

(2.1) Absolute contra-indications to hormone replacement therapy

Absolute contra-indications to HRT are existing breast carcinoma, existing endometrial carcinoma, venous thrombosis, and acute liver disease.

(3) Prescription of hormone replacement therapy

An algorithm for the prescription of HRT is shown in the Figure. For the purpose of hormone replacement, oestrogen may be administered orally, percutaneously, transdermally, or by using a subcutaneous implant. 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 that can in theory be affected by the hepatic 'first pass' effect of



* HRT hormone replacement therapy

Fig. An algorithm for the administration of hormone replacement therapy

Table 1. Examples of hormone preparations available in Hong Kong*

(1a) Unopposed oestrogen therapy		
Route	Generic drug (normal dosage)	Trade name (manufacturer)
Oral	Conjugated equine oestrogens (0.625 mg/d)	Premarin (Wyeth)
Oral	Oestradiol (2 mg/d)	Estrofem (Novo Nordisk)
Oral	Oestradiol valerate (2 mg/d)	Progynova (Schering AG)
Percutaneous gel	Oestradiol gel (2.5 g/d)	Oestrogel (Hoechst Marion Roussel)
Percutaneous patch	Oestradiol (two 4-mg patches per week)	Dermestril (Sanofi Winthrop) or Estraderm TTS (Novartis)
(1b) Combined cyclical (sequential) hormone replacement therapy		
Route	Generic drug (normal dosage)	Trade name
Oral	Oestradiol (2 mg/d) + dydrogesterone (10 mg/d, 14/28 days)	Femoston (Solvay)
Oral	Oestradiol (2 mg/d, 22 days; 1 mg/d, 6 days) + norethisterone acetate (1 mg/d, 10/28 days)	Trisequens (Novo Nordisk)
Oral	Oestradiol valerate (2 mg/d, 21 days) + cyproterone acetate (1 mg/d, 10/28 days)	Climen (Schering AG)
Oral	Conjugated equine oestrogens (0.625 mg/d, 21/28 days) + medrogestone (5 mg/d, 10/28 days)	Prempak (Wyeth)
Oral	Conjugated equine oestrogens (0.625 mg/d) + medroxyprogesterone acetate (5 mg/d, 14/28 days)	Premelle Cycle (Wyeth)
Percutaneous patch	Oestradiol (two 4-mg patches per week for 2 weeks) followed by patches containing oestradiol (10 mg/d) + norethisterone acetate (30 mg/d) [two patches per week for 2 weeks]	Estracomb TTS (Novartis)
(1c) Continuous combined hormone replacement therapy		
Route	Generic drug (normal dosage)	Trade name
Oral	Conjugated equine oestrogens (0.625 mg/d) + medroxyprogesteron acetate (2.5 mg/d)	Premelle (Wyeth)
Oral	Oestradiol (2 mg/d) + norethisterone acetate 1 mg/d)	Kliogest (Novo Nordisk)
Oral	Tibolone (2.5 mg/d)	Livial (Organon)

* As of 1 January 1999

oral oestrogens may be better treated by giving non-oral preparations. Such medical conditions include diabetes mellitus, hypertension, hypertriglyceridaemia, and a history of venous thrombosis.

(3.1) Unopposed oestrogen therapy

Unopposed oestrogen therapy implies the use of oestrogen without a progestogen (Table 1a). In 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.[8] The prescription of oestrogen as well as progestogen is referred to as combined HRT, and this combination may be given either cyclically (sequentially) or continuously.

(3.2) Combined cyclical (sequential) hormone replacement therapy

A cyclical (sequential) regimen implies that a progestogen is given on a cyclical basis (in addition to oestrogen) [Table 1b]. The 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). In a cyclical regimen, oestrogen is usually prescribed for 21 or 28 days while 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 hormone replacement therapy

Continuous combined HRT can be given to women with an established menopause (>2 years), in which case both the oestrogen and a progestogen are given on a daily basis (Table 1c). The aim of using such a regimen is for these women to remain amenorrhoeic. Spotting is common during the first few months of treatment. An alternative to continuous combined HRT is the use of tibolone, a synthetic agent that has weak oestrogenic, androgenic, and progestogenic properties. This drug can be used under the same circumstances as continuous combined oestrogen with a progestogen.

(3.4) Selective estrogen receptor modulators

Recent data on a new class of drugs referred to as selective estrogen receptor modulators (SERMs) have suggested that these drugs reduce the risk of breast and endometrial cancer.[9] Although SERMs have a beneficial effect on the serum lipid level and BMD, they have little or no therapeutic effect on acute menopausal symptoms. These drugs may thus be desirable for asymptomatic women who have a fear of breast cancer or those with risk factor(s) for the development of breast cancer. Selective estrogen receptor modulators may be prescribed whether or not the uterus is present.

(3.5) Duration of hormone replacement therapy

There are no rules regarding the duration of HRT. While the treatment continues, the beneficial effects of HRT will be maintained. Studies on the effect of long-term treatment on breast cancer risks are currently underway.

(4) Management of the menopause

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

In addition to using HRT, attention to life-style factors that promote good health should be encouraged. These factors include weight control and regular weight-bearing exercise.

(4.1) Monitoring of women receiving hormone replacement therapy

Cervical smears should be performed routinely as for

Table 2. Follow-up of women receiving hormone replacement therapy

Visit	Tests
At first visit	Blood pressure measurement; monitoring of levels of follicle-stimulating hormone, luteinizing hormone, and oestradiol to confirm menopause (if clinical features are atypical); lipid profile; liver function tests; bone biochemistry; mammography; urinanalysis
At each visit	Urinanalysis; blood pressure measurement
Every 2 years	Physical examination; lipid profile; liver function tests; determination of fasting glucose level; mammography
As indicated	Bone mineral density studies

all women with a uterus. Compliance with treatment symptom control, side effects (if any), and the bleeding pattern of those receiving combined treatment should be noted at each visit. The examinations and investigations shown in Table 2 are commonly performed, but there is no universal agreement as to which of them are essential.

(4.2) Management of irregular bleeding during hormone replacement therapy

(4.2.1) Bleeding during combined cyclical hormone replacement therapy

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

(4.2.2) Bleeding during continuous combined hormone replacement therapy

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 develop irregular bleeding but who were previously amenorrhoeic when using this regimen.

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