

**Audit protocol for management of Hormone replacement
therapy in General practice**

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Introduction

The field of menopause management is changing rapidly. The pros and cons of all treatments, including lifestyle changes and medication must be explained to women in order to make an informed, evidence based choice about the treatment.

In Hong Kong, the relatively small number of women using hormone replacement therapy is likely to result from two main factors. The first of these is the low incidence of acute menopausal symptoms. This was confirmed in a prospective study of Chinese women undergoing a surgical menopause, where the incidence of hot flushes was 24.2%, which is considerably lower than the 70% or so which may be expected in Caucasians (1). In addition, Chinese women in Hong Kong have very little knowledge of the effects of the menopause or the treatments which are available (2). The combination of a low incidence of symptoms and a lack of awareness of the possible long-term complications of the menopause means that Chinese women in Hong Kong may be less likely to seek advice about the menopause from a medical professional than Caucasian women.

The cost of treatment is unlikely to be contributing to the low number of women using HRT. The cost of a visit to a Hospital Authority outpatient clinic is \$44 (approximately USD 5.68). This sum includes the cost of drugs which can be prescribed for six months at each visit. It is difficult to estimate the number of postmenopausal women in Hong Kong who are using hormone replacement therapy. Unofficial estimates suggest that the figure lies somewhere between 3 and 6%. A wide range of preparations have been approved and are readily available. Conjugated equine oestrogens (Premarin, Wyeth; Conjugated Oestrogens Jean-Marie, Jean-Marie) are the most commonly prescribed oral oestrogens, but oral estradiol (Estrofem, Novo Nordisk; Progynova, Schering) and oral estriol (Ovestin, Organon) are also used. Non-oral oestrogen is available in patches (Estraderm TTS, Ciba) and as a percutaneous gel (Oestrogel, Besins). There are a wide variety of combined cyclical oral preparations (Prempak, Wyeth; Trisequens, Novo Nordisk; Femoston, Solvay; Climen, Schering; Dilena, Organon) and continuous combined treatment is also available (Kliogest, Novo Nordisk, Livial, Organon).

Combined treatment is also available in patches (Estracomb TTS, Ciba). Another unofficial estimate suggests that sales of hormone replacement therapy products currently amount to approximately HKD 10,867,000 per annum, and are increasing by more than 25% each year (3).

Hormone replacement therapy- Summary of Criteria

- 1. The records show whether a woman have an intact uterus and women with an intact uterus should not be offered un-opposed oestrogen.**
- 2. The records show the indications for hormone replacement therapy:**
Patients suffering from vasomotor symptoms at/after menopause could be offered HRT.
- 3. The records show that absolute contraindications are assessed, which include existing breast cancer, acute liver disease, venous thrombosis and existing endometrial cancer.**
- 4. The records show that the following conditions should not be offered HRT:**
 - (i) Women with osteoporosis should not be offered HRT as first line treatment**
 - (ii) HRT should not be given for primary prevention of cardiovascular disease and cerebrovascular disease**
- 5. The records show that patients on HRT should be advised on regular mammography screening.**
- 6. The records show that women starting or continuing HRT should be counseled with regard to the perceived benefits and possible risks.**

For all women on HRT who have attended the HKFC clinic for HRT prescription within recent 12 months:

Criteria 1

The records show whether a woman have an intact uterus and women with an intact uterus should not be offered un-opposed oestrogen.

Women with an intact uterus experience an increased risk of irregular bleeding, endometrial hyperplasia and endometrial cancer if they use unopposed oestrogens (4) A meta-analysis of 30 observational studies demonstrated an overall relative risk of endometrial cancer of 2.3 for oestrogen users compared with non-users, rising to 9.5 after 10 years of use. (5)

Continuous or cyclical (for 12 days each month) progestogen used in conjunction with the oestrogens eliminates the increased risk. (6,7). Taking progestogen for only 10 days each cycle reduces but does not eliminate the increased risk. (8) Oestradiol implants necessitate the use of long term progestogens.

(9)

Criteria 2

The records show the indications for hormone replacement therapy:

Patients suffering from vasomotor symptoms at/after menopause could be offered HRT.

Hormone replacement therapy is effective for the relief of vasomotor symptoms, insomnia and urogenital atrophy associated with menopause. (10,11,12) Oral HRT is highly effective in alleviating hot flushes and night sweats. (13)

Criteria 3

The records show that absolute contraindications are assessed, which include existing breast cancer, acute liver disease, venous thrombosis and existing endometrial cancer.

The absolute contraindications to the use of HRT include existing breast carcinoma, existing endometrial carcinoma, venous thrombosis and acute liver disease. (14)

Criteria 4

The records show that the following conditions should not be offered HRT:

- (i) Women with osteoporosis should not be offered HRT as first line treatment**
- (ii) HRT should not be given for primary prevention of cardiovascular disease and cerebrovascular disease**

Million Women Study has shown an increase in fatal disease with a relative risk of 1.22 of death from breast cancer over controls. Current users of oestrogen only had a relative risk of breast cancer of 1.30, whereas the combined oestrogen-progestogen preparations have a relative risk of 2.00. (15) The oestrogen-progestogen arm of the WHI study was stopped because the group reached the limit on excess risk of breast cancer, however the oestrogen alone arm of the trial had no significant increased risk of breast cancer and it was later stopped due to increased risk of stroke. (16) The Committee on Safety of Medicines has concluded that HRT should no longer be recommended as first line therapy for preventing osteoporosis, due to the increased breast cancer risk on the long term treatment required to have a lasting effect on bone metabolism. (17)

Large observational studies show that HRT users have a lower risk of death from cardiovascular disease than those who have never taken HRT. (18) However, from HERS study, the first prospective randomized controlled trial, was stopped after 4.1 years of active treatment because the data showed that in the first year women on HRT suffered more coronary events than the placebo group. (19) The Women' Health Initiative Study was prematurely stopped after 5.2 years because it was deemed the women given combined HRT suffered more harm than good. (16) The recommendations after the HERS and WHI studies are that postmenopausal women should not put on HRT to reduce the risk of coronary heart disease.

The Canadian Task Force on Preventive Health Care concludes that there is fair evidence to recommend against the use of hormone replacement therapy (HRT) for the primary prevention of myocardial infarction and death from cardiovascular disease in perimenopausal women without established coronary artery disease (CAD) (grade D recommendation). There is insufficient evidence to make a recommendation on the use of HRT for the primary prevention of stroke and death from cerebrovascular disease. However, because stroke is a major cause of morbidity and death among Canadian women, other beneficial preventive measures, such as aggressive treatment of hypertension, should be used rather than HRT. (20) Given the balance of harms and benefits, the Canadian Task Force on Preventive Health Care recommends against the use of combined estrogen–progestin therapy and estrogen-only therapy for the primary prevention of chronic diseases such as osteoporosis or cardiovascular disease/cerebrovascular disease in menopausal women (grade D recommendation). (21)

Criteria 5

The records show that patients on HRT should be advised on regular mammography screening.

International data based on 52705 breast cancer patients and 108411 controls concluded that the risk of breast cancer increases with duration of use of HRT. (22) This excess risk reduces when therapy is withdrawn and disappears 5 years after stopping HRT. Between the ages of 50 and 70 years the cumulative incidence of breast cancer is 45 per 1000 in never-users of HRT. This risk is increased by 2 cases per 1000 women after 5 years of use, by 6 cases per 1000 after 10 years of use and by 12 cases per 1000 after 15 years of use. Swedish studies have confirmed an RR of between 1.4 and 2.43 after 10 years of HRT use. (23,24) Progestins do not reduce the risk and there is some evidence that they may actually increase it. (25)

New data from the Million Women Study has shown an increase in fatal disease with a relative risk of 1.22 of death from breast cancer over controls. Current users of oestrogen only had a relative risk of breast cancer of 1.30, whereas the combined oestrogen-progestogen preparations have a relative risk of 2.00. (15) The oestrogen-progestogen arm of the WHI study was stopped because the group reached the limit on excess risk of breast cancer, however the oestrogen alone arm of the trial had no significant increased risk of breast cancer and it was later stopped due to increased risk of stroke. (16)

Criteria 6

The records show that women starting or continuing HRT should be counseled with regard to the perceived benefits and possible risks.

Early studies demonstrated accelerated blood clotting in women on conjugated equine oestrogen (26,27) and an increased risk of thromboembolism in women currently taking HR was found in 1996. (28,29,30,31) A relative risk of venous thromboembolism in women on HRT between 2.1 and 3.6 has been reported in case controlled studies. (28,29,30,31,32,33) The Committee on Safety of Medicines advised that the baseline risk of thromboembolism for non-users of HRT is 1 per 10000 per year which increased to 3 per 10000 per year for current users of HRT. (34)

In the Women's Health Initiative study, the primary outcome measure was coronary heart disease. After 5.2 years of follow-up, the trial was stopped as there was an increased risk of coronary heart disease (hazard ratio 1.29, 95%CI 1.02-1.63), stroke (hazard ratio 1.41, 95%CI 1.07-1.85) and breast cancer (hazard ratio 1.26, 95%CI 1.0-1.59) as well as pulmonary embolism. (16)

For women who wish to alleviate menopausal symptoms using hormone replacement therapy (HRT), a discussion between the woman and her physician about the potential benefits and risks of HRT is warranted. (21)

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Prepared by Dr. LAI Wing Yiu

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