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What You Need To Know: Prescribing Hormone Replacement Therapy

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INTRODUCTION

The decision to use hormone replacement therapy (HRT) will be made by a woman for one of four reasons: (1) premature menopause, (2) symptoms from lowered or fluctuating oestrogen levels, (3) as treatment for established disease such as osteoporosis or coronary artery arteriosclerosis, (4) her belief in health or quality of life benefits. Possible permutations from the 3 groups of hormones (oestrogens, progestogens, androgens), the wide variety of available preparations, routes of administration, recommended dosages and treatment regimens are almost limitless.

In the fertile period of a woman's life the ovaries produce oestrogen continuously, progesterone cyclically and a relatively small amounts of androgens except when the steroid synthesis pathway is disturbed such as in polycystic ovarian syndrome. In HRT addition of progestogens has been shown to block effectively the increase in endometrial carcinoma associated with use of unopposed oestrogens[1] and is almost always given to unhysterectomised patients on HRT. Testosterone, when given with oestrogen, appears to have a beneficial effect on the libido and may also be used to counteract oestrogenic stimulation of residual endometrial cells if a patient has recently undergone hysterectomy and bilateral oophorectomy for symptomatic endometriosis.

HRT PREPARATIONS AVAILABLE IN SINGAPORE

Formulations of oestrogen available in Singapore include both oral and parenteral preparations[2]. Arguments have been raised both for and against the benefits of a "first pass" through the liver. Whilst some immediate degradation is avoided, stimulation of liver enzyme systems, for instance those raising in high density lipoproteins (HDL), may be reduced.

The distinction between "natural" (animal derived) oestrogen and "synthetic" (laboratory produced) oestradiol is rather artificial since a large percentage of oestrogen in Conjugated Equine Oestrogens (Premarin®) is structurally dissimilar to human oestradiol and metabolised more slowly, resulting in a much prolonged half life. Oral oestradiol is often presented as an ester to reduce gastric degradation (e.g. Progynova®, Climen®) but pure oestradiol is found in a micronised form in Estrofem®. Women with menopausal symptoms needing contraceptive protection may use combined oral pills provided they do not smoke nor have thrombogenic risk factors.

"Natural" progesterone is currently available orally as Utrogestan®. The majority of the scientific data on progestogen use come mainly from medroxy-progesterone acetate (Provera®) in the USA and norethisterone in Europe. The relative advantages of 19-nor testosterone progestogens against those derived from 17α-OH progesterone have been debated. The former seem to give better cycle control and to conserve bone while the latter do not antagonise the beneficial effect of oestrogens on HDL. The 'third generation' progestogens such as desogestrel and gestodene have never been released here for HRT and now probably never will be as a result of adverse findings in oral contraceptive pill studies.

Oestrogens and progestogens are both marketed separately, together in one pill, or in combination packs. The latter are easy to use and prescribe but lack the flexibility in dosage often necessary for an individual patient. Oral testosterone in combination with oestrogen (e.g. Estratest®, Mixogen®) is currently not available in Singapore.

DOSAGE

Before the association between endometrial cancer and oestrogen use had been recognised some women had taken very large doses of oestrogen (up to 6gm/day of Premarin) to eradicate all menopausal symptoms, with no apparent ill effects. More recently the usual dosage has been based on studies estimating bone mass preservation. Using this criterion a daily dose of 0.625 mg Premarin has become standard though some women require 0.9 mg or even 1.25 mg daily to reduce symptoms to a tolerable level. In fact up to 7% women continue to suffer significant bone loss if only treated at the 0.625mg/day level. The oestradiol equivalent dose is 2mg/day.

The HRT dose required will vary with the individual and with the purpose of medication. If treatment is to reduce intractable symptoms the dose should be set to a level that makes symptoms tolerable even if they are not eradicated altogether. On the other hand if the HRT is given in a symptom-free woman to prevent progression of osteoporosis in a patient with a family history of thrombosis or breast cancer, lower levels would seem appropriate. The

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pharmokinetics of oestrogen metabolism is complicated[3], and a dynamic relationship exists between precursors of oestradiol such as oestrone or metabolites such as oestrone sulphate. Oestradiol plasma levels equivalent to the normal range in pre-menopausal women (60-700pg/ml) can be achieved by any of the various available routes of administration. The current consensus of opinion is that it is the duration of cyclical progestogens (10 to 12 days) that gives protection against endometrial cancer rather than the dose which has been progressively reduced to 0.7-1mg norethisterone or 2.5mg medroxyprogesterone acetate.

REGIMENS

Cyclical 3 week treatment regimens with additional progestogen in the last 10 to 14 days are often prescribed in the USA but in Europe continuous oestrogen replacement is more common. There is however no evidence that significant symptoms return if an oestrogen free week is included[4].

Continuous combined oestrogen and progestrogen regimes to avoid withdrawal bleeding are used but often complicated by irregular spotting, particularly in perimenopausal women, which makes them less attractive. Tibilone (Livial®), a steroid with mixed oestrogenic, androgenic and progestational properties, is an available alternative. Use of progestogens only once every two or three months has also been advocated but whether the protective effect against endometrial cancer is reduced is not clear.

ALTERNATIVES

There is currently a significant movement towards the use of herbal medicines. Cimicifuga racemosa (Remifemin®) is a non-prescription drug which has recently been promoted to physicians while Evening Primrose Oil and Starflower Oil are available over the counter though randomised trials sometimes do not support efficacy. Phytoestrogens[5], (present in soy products etc.) are only weakly oestrogenic but may be protective for the breast and the cardiovascular system. The protective effect of tamoxifen against breast cancer has led to the development Selective Estrogen Receptor Modulators (e.g. Raloxifene®) which have different oestrogenic actions on different oestrogen sensitive organs.

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