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HORMONE REPLACEMENT THERAPY

SUMMARY

- **Hormone Replacement Therapy (HRT) is effective for the treatment of menopausal symptoms and the prevention of osteoporosis in at-risk women**
- **Use is associated with an increased risk of breast cancer, venous thromboembolism and endometrial cancer (concomitant progestogens lessen this risk)**
- **Recent studies have suggested an increased risk of cardiovascular disease with use of certain combination HRT preparations**
- **The risks and benefits should be determined at an individual level and discussed with the patient, with the need for continuation reviewed at least every 6 months**

INTRODUCTION

The World Health Organisation defines natural menopause as the permanent cessation of menstruation, determined retrospectively after 12 consecutive months of amenorrhoea, without any other cause[1].It results from ovarian failure and resultant oestrogen deficiency. Peri-menopause refers to the years around the menopause. It is reported that by 50 years of age, 75% of women have started or completed the menopause transition (38% peri-menopausal, 37% post-menopausal).

In Ireland, the current life expectancy for women is 79 years[2]. This means that the average woman lives for at least 30 years after menopause, a phase of life often associated with increasing rates of chronic illnesses, including cardiovascular disease (CVD), osteoporosis, cognitive decline and cancer[3]. Hormone replacement therapy (HRT) has been used for many decades in the management of menopausal symptoms and in the prevention of osteoporosis. It was thought to be protective against CVD[4] but recent large randomised controlled trials[5,6] suggested an increased risk of CVD with certain forms of HRT. This bulletin will evaluate the current knowledge regarding the benefits and risks of HRT in peri- and post-menopausal women.

HRT PREPARATIONS

There are 2 main types of HRT. A combination of oestrogen and progestogen is used in women with an intact uterus (because of the risk of endometrial carcinoma with unopposed oestrogen), whereas oestrogen monotherapy can be given to hysterectomised women. Approximately 30 preparations of HRT are currently available for use in Ireland. The preparation to be used is usually determined by patient preference.

Oral preparations of combination HRT are commonly used. A continuous (no "period") combined daily dose of oestrogen and progestogen (cHRT) is normally used in women who have reached menopause. Sequential or cyclic HRT (sHRT), consisting of daily oestrogen with 10-14 days of a progestogen over a 28-day cycle, is normally used in perimenopausal women. This is associated with a regular bleed. cHRT is not suitable for use in the peri-menopause or within 12 months of the last menstrual period as irregular bleeding may occur; iregular it persists endometrial abnormality should be ruled out and sHRT should be given[7].

Transdermal (patch) formulations are also used; some preparations contain both hormones, while others contain oestrogen only and must be used in association with oral administration of a progestogen, if required.

Vaginal formulations are available for the management of local symptoms.

Oestrogen monotherapy is available in oral, transdermal, nasal spray and gel formulations but should only be used in hysterectomised women.

Tibolone is an oral agent with oestrogenic, progestogenic and weak androgenic properties. It does not require combination with a progestogen. It should only be used in women who have reached menopause (as irregular bleeding may occur in women who are still producing some endogenous oestrogen)[7].

INDICATIONS FOR HRT USE

1. Menopausal Symptoms

Evidence. Menopausal symptoms include flushing, sweating, palpitations, anxiety, irritability, genitourinary symptoms and insomnia[8]. They occur during the perimenopausal years in up to 80% of women and severity is linked to certain factors such as smoking, low body weight, low levels of exercise and lower socio-economic class[1]. Surgery-induced menopause is associated with more severe symptoms in almost all patients. Relief of menopausal symptoms is the commonest reason for starting HRT. It has been reported that HRT improves symptoms in the vast majority of patients who receive it[9,10]. It is uncertain whether HRT improves all menopausal symptoms or just the "vasomotor" symptoms – e.g. relieving hot flushes and sweats may improve sleep, which improves mood symptoms[9]. It is reported that vaginal oestrogen is as effective as oral or transdermal oestrogen for the management of genitourinary symptoms[3].
There are no long-term data to show beneficial effects for HRT on quality of life, in the absence of menopausal symptoms[11]. A recent study, carried out in over 16,000 post-menopausal women (aged 50-79 years, mean 63 years) showed no clinically meaningful beneficial effect of combined HRT on health-related quality of life over 1-3 years' treatment, compared with placebo[12]. Assessment included depression scores, functional status, cognitive and sexual functioning, but did not include items such as self-perceptions of youthfulness or skin tone. The lack of a protective effect against cognitive decline in postmenopausal women with HRT was also noted in a prospective observational study, which evaluated over 9,600 older women, over a 4-6 year follow-up period, using a variety of HRT regimens[13].

Advice. Use of HRT is currently recommended for the management of menopausal symptoms in the absence of contraindications (e.g. history of CVD, venous thromboembolism or breast cancer)[11]. Since menopausal symptoms are transient (usually lasting no more than 2-3 years), the need for continuing treatment should be re-evaluated on a regular basis (at least every 6 months).

TABLE 1

INDICATION FOR HRT USE[9]		
MENOPAUSAL SYMPTOMS	**NO MENOPAUSAL SYMPTOMS**	
• Discuss HRT with patient (if no contraindications for use) • Prescribe HRT on short- term basis • Review patient regularly • Evaluate continuing need for HRT	***Risk factors for osteoporosis*** • Discuss HRT and alternatives with patient (if no contraindications for use) • Review patient regularly • Evaluate continuing benefit/risk of HRT	***No risk factors for osteoporosis*** • HRT not indicated for use

2. Osteoporosis

Evidence. It is estimated that one third of women over the age of 50 years will sustain a fracture, with osteopenia being a major risk factor[9]. Some women are at greater risk – due to premature menopause, smoking, excessive alcohol intake, positive family history or use of steroids for > 6 months. Oestrogen inhibits the age-related loss of bone that occurs in most women after the menopause[3]. A meta-analysis of randomised controlled trials[14] showed a significant reduction in fractures with use of HRT. However, the benefits were less in women greater than 60 years. The Women's Health Initiative (WHI) study[6] also reported a reduction in total fractures of 24% with hip and clinical vertebral fractures reduced by one third, compared with placebo, during a 5.2 year period of follow-up.
Discontinuation of HRT results in resumption of bone loss similar to that in non-HRT users. Furthermore a recent study which evaluated bone mineral density (BMD) in HRT users over a 7 year period, suggested that use of HRT beyond 3 years does not lead to additional gain in BMD[15].

Advice. HRT is recommended for the prevention of osteoporosis in postmenopausal women judged to be at particular risk of fractures. In light of the availability of other agents (such as bisphosphonates and raloxifene) for the management of osteoporosis, it is recommended that the potential benefits and risks of HRT be determined on an individual patient basis.

POTENTIAL PROBLEMS WITH USE OF HRT

1. Cardiovascular disease(CVD)

Evidence. CVD rarely affects women before the menopause, suggesting that oestrogen deficiency may play a role in the aetiology of the disease in post-menopausal years. Observational studies suggested a protective role against CVD for HRT[4], but this finding was not borne out in 2 randomised controlled trials, HERS and WHI. HERS[5] evaluated the risk of cardiovascular events, in almost 3,000 postmenopausal women (mean age 65 years) with known coronary heart disease (CHD), over a follow-up of 6.8 years. Results showed no overall difference between combination HRT and placebo for CHD events (non-fatal myocardial infarction, CHD-related death) or any other secondary cardiovascular outcome. More CHD events were reported during the first year of treatment and fewer CHD events in years 3-5, compared to placebo.
WHI[6] randomised over 16,000 postmenopausal women (50-79 years) with an intact uterus and without prior known CVD, to receive either combination HRT or placebo. The primary outcome was the effect of HRT on CHD. The study was discontinued early (after 5.2 years of follow-up) because of adverse findings for breast cancer with HRT (see below) but results available at that time showed that HRT was associated with a 29% increased risk of CHD (corresponding to an absolute increased risk of 7 CHD events per 10,000 person years). There was no overall increase in mortality during the period of study. The recommendation from these 2 studies was that combination HRT should not be used for primary or secondary prevention of CHD.
The results from these 2 trials are at variance with results from observational studies[4], which had suggested a potential protective effect against CHD with HRT. The discrepancy is thought to be due to the "healthy user" effect whereby women in the observational studies were more likely to have followed a healthy lifestyle and therefore to have a lower risk of CHD than the general female population of the same age[16]. Both HERS and WHI used a form of combination HRT (oestrogen 0.625mg and medroxyprogesterone acetate 2.5mg/day) that is not available in Ireland. Moreover, the mean age in WHI was 63 years, which is older than the patients seeking HRT in other countries[17]. Additional studies are ongoing to further elucidate this issue.

Advice. It is not known how these results may be extrapolated to other forms of combination HRT, such as those currently licensed in Ireland. However in light of these findings the use of HRT, either for prevention of CVD or its use in women with a high risk of CVD is currently not recommended, because the potential harm is thought to outweigh the potential benefit[9,11,18].

2. Venous Thromboembolism (VTE)

Evidence. Both observational studies and randomised controlled trials have reported a 2-3 fold increased risk of VTE with use of HRT[2,6,19]. Because the absolute risk of VTE is small in women over 50 years of age, the estimated absolute increased risk corresponds to approximately 20 extra cases per 10,000 person years for VTE and 6-8 per 10,000 for pulmonary embolus[6,9]. The risk is greater in the first year of use and in those with predisposing factors (positive family history, obesity, surgery, immobility, severe varicose veins).

Advice HRT is contraindicated in women with a previous history of VTE and should be used with caution in women at increased risk of VTE.

3. Breast Cancer

Evidence. A large meta-analysis of 51 observational studies has shown that the risk of breast cancer appears to increase for each year of use of HRT, becoming statistically significant (compared to non-use) after 5 years of treatment[20]. This excess risk translates into 2 extra cases of breast cancer per 1000 women on HRT for 5 years and 6 extra cases per 1000 after 10 years of use. In the WHI study[6], the combination HRT used was associated with a 26% increased risk of developing breast cancer compared with placebo after 5.2 years of use. This finding resulted in the early discontinuation of this part of the WHI study. The HERS study also showed a 27% increased risk of breast cancer after 6.8 years of follow-up, although this finding was not statistically significant. Neither study showed an increased mortality from breast cancer during the study.
The increased risk of breast cancer falls following discontinuation of HRT and returns to baseline after 5 years[9].

The risk of breast cancer with oestrogen monotherapy appears to be less; more information will be available from the WHI oestrogen monotherapy versus placebo study, which is still ongoing.

Advice. Prolonged use of HRT (> 5 years) is not recommended because of the increased risk of breast cancer. HRT is currently contraindicated in women with a history of breast cancer.

4. Endometrial Cancer

Evidence. It has been shown in over 30 observational studies that long-term use of unopposed oestrogen monotherapy is associated with a 8-10 fold increased risk of endometrial cancer, which results in an excess of 46 cases per 10,000 women after 10 years of use[21]. The addition of a sufficient dose of a progestogen to oppose the effects of oestrogen on the endometrium eliminates the risk.

Advice. Combination HRT is the treatment of choice for women with an intact uterus[3].

OTHER SAFETY ADVICE FOR USE OF HRT[7]

There is a **modest increased risk of stroke** with use of HRT– 1 additional case per 1000 women aged 50-60 years using HRT for 5 years. It would appear from the WHI study that this is not associated with increased blood pressure and that the risk is greater with longer duration of use[6].There appears to be a
slightly increased risk of ovarian cancer with long-term use of oestrogen monotherapy[22]. The risks with combination HRT are not fully evaluated.
HRT does not provide contraception; a woman is considered potentially fertile for 2 years after her last menstrual period if she is < 50 years and for 1 year if she is > 50 years. Therefore a woman requiring HRT should also be advised to use non-hormonal contraceptive methods.
HRT should be stopped immediately if any of the following occur - sudden severe chest pain; sudden breathlessness (+/- cough and haemoptysis); severe unexplained calf pain; severe stomach pain; severe headache or other severe neurological symptoms; jaundice or hepatitis; hypertension (BP>160/100mmHg); severe depression – and the causes fully investigated.
HRT should be discontinued 4-6 weeks before major elective surgery and should not be resumed until after full mobilisation has occurred.

CONCLUSIONS

HRT can be used to treat menopausal symptoms and prevent osteoporosis. In light of the known safety profile with its use, it is recommended that the potential risks and benefits of HRT are determined on an individual patient basis. The need for continuing treatment should be reviewed regularly and at least every 6 months.

TABLE 2

MONTHLY GMS COST OF COMMONLY USED HRT PREPARATIONS (JAN. 2003)

Type of preparation	Constituents	€
cHRT (oral)	Oestradiol 2mg + norethisterone acetate 1mg	6.77
Oestrogen (oral)	Oestrogen* 0.625mg-1.25mg	2.93-3.95
sHRT (oral)	Oestrogen* 0.625mg / Oestrogen* 0.625mg + medroxyprogesteroneacetate*** 10mg	8.72
Oestrogen (patch)	Oestradiol 25/50/100mcg**	7.28-9.85
Combination patch	Oestradiol**50mcg / Oestradiol** 50mcg + norethisterone*** 250mcg	13.21

*** conjugated** ****daily dose equivalent** ***** progestogen administered for 2 weeks of 4 week cycle**

List of references available on request