

## **HORMONE REPLACEMENT THERAPY (HRT)**

### **SUMMARY**

- HRT offers relief from menopausal symptoms.
- Potential benefits are reducing the risks of coronary heart disease and osteoporosis.
- Potential risks are increased malignancy of breast and uterus, although concomitant progestogens reduce the risk of uterine cancer.
- The risks and benefits should be discussed and a decision made on an individual patient basis.

Hormone replacement therapy (HRT) has been used for several decades, but there is a surprising lack of consensus about when and how to use it. The initial goal of oestrogen replacement therapy was to alleviate menopausal symptoms. More recently, the possibility has emerged that oestrogen can reduce morbidity and mortality from coronary heart disease and osteoporosis. However, women and their physicians must balance these apparent benefits against the possibility that oestrogen therapy might increase the incidence of cancer of the breast and uterus. Assessing the patients overall risk of breast cancer, osteoporosis or cardiovascular disease may be the key to deciding whether or not to prescribe long term HRT.

### **HRT AND MENOPAUSAL SYMPTOMS**

Up to 75% of post-menopausal women get symptoms of the menopause<sup>1</sup> and approximately 30% seek medical help. Only 9% of females in the age group 40 - 64 years take HRT but many stop within a few months due to return of menstrual periods or fear of cancer. Vasomotor symptoms including flushing, night sweats and palpitations together with genito-urinary tract symptoms such as dysuria, frequency and dyspareunia cause great concern for this group of patients. HRT can relieve these symptoms but may need to be taken for three months to obtain full effect. HRT, if taken solely for relief of symptoms should be reduced or discontinued every six months to see if it is still required<sup>2</sup>.

### **HRT AND OSTEOPOROSIS**

A 50 year old woman has a 15% life time probability of suffering a hip fracture at an average age of 79 years<sup>3</sup>. HRT is recommended for the prevention of osteoporosis in women with premature menopause and in post-menopausal women who have several risk factors for osteoporosis. These risk factors include:- age greater than 60 years, recent corticosteroid therapy, any disease predisposing to osteoporosis, family history, low body mass index, lack of exercise, alcoholism, smoking or fracture of hip or forearm before 65 years of age<sup>4</sup>. Bone mass density may help identify women at highest risk of osteoporosis. Oestrogen replacement therapy prevents the accelerated bone loss which normally accompanies the menopause<sup>5</sup> and in addition actually increases the bone density in those at increased risk of fracture. Treatment should be started as soon as menopause is diagnosed and given for at least 5 years and preferably 10 years<sup>6</sup> because short term HRT does not protect from osteoporosis or reduce the risk of fracture<sup>7</sup>. Limited but consistent observational evidence shows that oestrogen therapy alone reduces the risk of hip fractures in post-menopausal women by about 25% and that combined oestrogen/progestogen therapy is probably at least as effective as unopposed oestrogen. Most studies on osteoporosis used conjugated oestrogen at doses of 0.625mg daily<sup>3</sup>. Discontinuation of treatment is followed by immediate resumption of bone loss and some researchers suggest that HRT be continued indefinitely in order to decrease the risk of fracture, but the safety of long term HRT is not established<sup>8</sup>.

### **HRT AND CARDIOVASCULAR SYSTEM**

A 50 year old woman has a 46% life-time probability of developing coronary heart disease (CHD) and death from CHD occurs on average at 74 years of age<sup>3</sup>. Reducing the risk of CHD has been attributed to the use of oestrogen<sup>9</sup> which may be the most significant long term benefit of HRT because CHD is the greatest cause of death in post-menopausal women. Oestrogen elevates high density lipoproteins (HDL) and reduces low density lipoproteins (LDL)<sup>10</sup>, other beneficial effects may include a direct effect on the

atherosclerotic process and a vasodilatory effect on the coronary arteries. Most studies demonstrating these effects used conjugated equine oestrogen alone in doses of 0.625-1.25mg/daily. The extent to which the beneficial effects of oestrogen are reduced depends on the type, dose and duration of progestogen added. Several studies<sup>11,12,13</sup> confirm that unopposed oestrogen is the optimal choice for elevating HDL levels but this benefit is reduced when cyclical or continuous progestogen is added to the oestrogen. In addition HRT elevates triglyceride levels. However, no clinical trial has shown that increasing HDL or reducing LDL levels alters the risk of CHD in women and further evidence is required before HRT is recommended for CHD prevention. Currently HRT is not licensed for this indication.

## **HRT AND BREAST CANCER**

A 50 year old woman has a 10% probability of developing breast cancer at an average age of 69 years<sup>3</sup>. More than 30 epidemiological studies have explored the relationship between HRT and breast cancer. Despite several attempts to summarise available evidence in overviews and meta-analyses there is considerable uncertainty as to whether HRT increases breast cancer risk. Generally it is believed that current users of HRT over five years duration increase their risk of getting breast cancer by about 10% and this applies to patients on oestrogen alone as well as combined oestrogen/progestogen preparations<sup>14,15,16</sup>. In addition, the increased risk of breast cancer was even greater among older women in the 60-64 year age group<sup>15</sup>. Even patients who have stopped HRT are at increased risk of breast cancer in the short and medium term<sup>16</sup>. It has been suggested that HRT brings on a non-aggressive breast cancer which has a good prognosis<sup>17</sup> and so is not associated with increased mortality. Careful selection of low risk patients will reduce the incidence of breast cancer due to HRT.

## **HRT AND ENDOMETRIAL CANCER**

A 50 year old woman has a 2.6% life time probability of developing cancer of the endometrium at an average age of 68 years<sup>3</sup>. The increased risk of endometrial cancer due to unopposed oestrogen in HRT is now well established<sup>3,18,19</sup> which may be increased as much as ten fold if the oestrogen is taken for life. Short term use of HRT (1-5 years) is associated with a three fold increase in cancer and this risk can persist for five years after stopping the unopposed oestrogen. Progestogen protects the endometrium and reduces the incidence of endometrial cancer; women with an intact uterus should take cyclical progestogen<sup>20</sup>. The duration of progestogen administered per cycle is of paramount importance and should be taken for twelve days each month<sup>1</sup>. Some clinicians use continuous progestogen which renders the endometrium atrophic and avoids menstrual bleeding in up to 75% of patients after six months treatment<sup>21</sup>.

## **HRT PREPARATIONS**

There are over 20 different preparations available which may be administered in the following routes:-

Vaginal: Useful for short term treatment of urogenital symptoms.

Oral: The most widely used form of HRT. Oestrogen should be administered alone if the patient has had a hysterectomy or in combination with progestogen if the uterus is present. There are several brands of combined oestrogen and progestogen preparations available. Some provide continuous oestrogen with cyclical progestogen e.g. Menophase, Prempak C and Trisequens. Kliogest offers continuous oestrogen and progestogen. Cycloprogynova provides an oestrogen free week but there is no evidence that this is needed. There is also no evidence that varying an oestrogen dose as in Menophase or Trisequens is necessary. Tibolone (Livial) with weak oestrogenic, progestogenic and androgenic properties does not stimulate the endometrium and is therefore not associated with recurrence of withdrawal bleeds which may be an advantage for women with an intact uterus. It should not be used until one year after the last menstrual cycle, since vaginal bleeding may occur in women who still produce some endogenous oestrogen. However up to 15% of women experience irregular bleeding while taking tibolone<sup>22</sup>. There is no point in giving tibolone to women who have had a

hysterectomy. Tibolone is expensive, its long term profile not yet established compared to conventional HRT and may not offer protection against coronary heart disease<sup>22</sup>.

**Transdermal:** As effective as oral oestrogen but more expensive. The oestrogen can be given alone; oral progestogen or transdermal progestogen added if required.

**Sub-cutaneous:** Depot implants of oestradiol avoids the need for continuous oral oestrogen but still requires opposing progestogen in women with a uterus. It is not a first choice option but may suit some patients.

Physical and gynaecological examination should precede the prescribing of HRT with regular review of the patient every 6-12 months.

## **CONTRAINDICATIONS**

As the understanding of HRT has improved the number of contraindications to its use have declined. Absolute contraindications include, endometrial cancer, breast cancer, pregnancy, undiagnosed abnormal vaginal bleeding and severe active liver disease with abnormal liver function tests. The presence of a history of deep vein thrombosis (DVT), CHD, hypertension, smoking or diabetes may not now be regarded as reasons to avoid HRT. Ischaemic heart disease or the presence of risk factors for IHD could be regarded as reasons to commence HRT. A single episode of DVT is not an absolute contraindication if the DVT developed due to a precipitating cause such as, surgery or pregnancy. Where there is a history of repeated DVT's or a permanent increased risk of thrombosis then HRT should be avoided. For further information on the contraindications of the individual preparations the prescriber should refer to the drug data sheet.

## **SIDE EFFECTS**

Oestrogenic side-effects include breast tenderness, epigastric discomfort, nausea and leg cramps. Progestogenic side-effects include breast tenderness, bloated feeling, mood swings, anxiety, irritability and greasy skin and a change of preparation may reduce some of these. Breakthrough bleeding is common in the first few cycles and can be managed by changing preparations, but if persistent requires further investigation.

## **DRUG INTERACTIONS**

Patients on HRT may experience breakthrough bleeding if antibiotics are taken. Barbiturates, phenytoin and carbamazepine which are liver enzyme inducers may lead to increased oestrogen clearance<sup>23</sup>.

## **CONCLUSION**

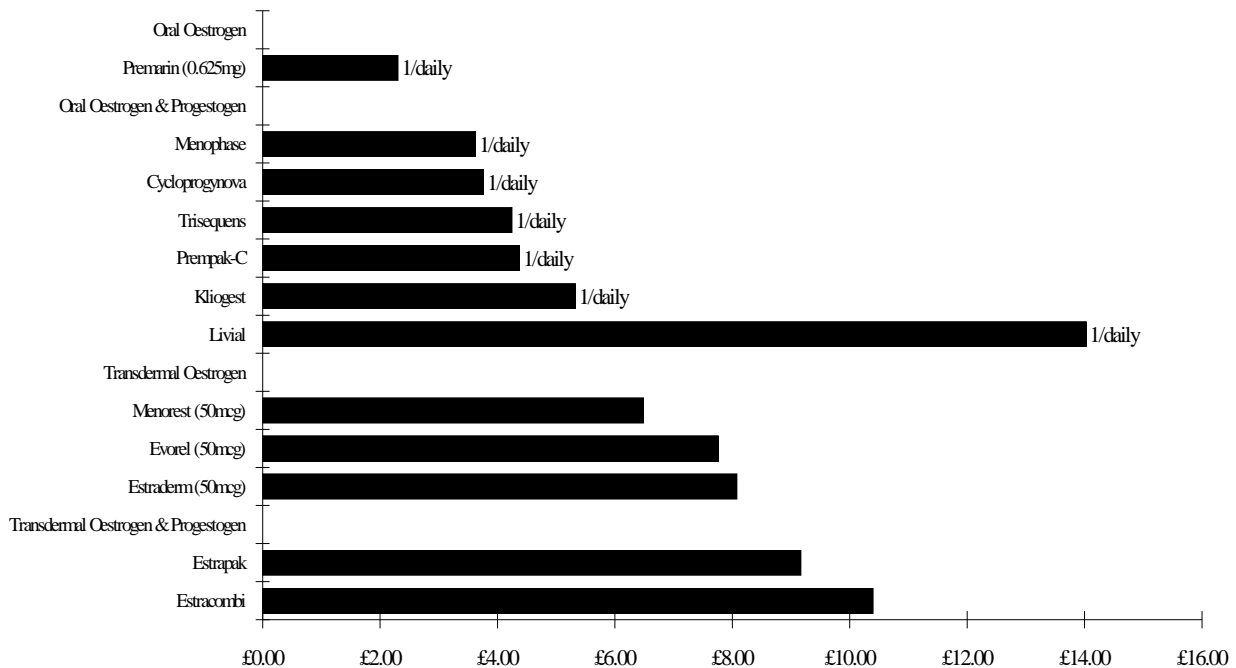
Apart from short term treatment of menopausal symptoms it is not yet clear if the benefits outweigh the risks in women who have low risk of heart disease. Available guidelines<sup>24</sup> suggest consideration of the risks and benefits for each individual, with clear discussion and recording of these discussions. Selective prescribing of HRT for those at high risk of CHD or fracture may prove to be the best approach. Whether HRT actually prolongs life or not is uncertain; it may improve the quality of life in a person at high risk of morbidity from a fracture or myocardial infarction. However, the final decision to use HRT will depend on the patient and also on how much the future is to be discounted<sup>25</sup> since the median age at diagnosis of breast cancer is 69 years, myocardial infarction 74 years and hip fracture 79 years<sup>3</sup>. For some the avoidance of breast cancer and endometrial cancer may be more important than the prevention of heart disease or osteoporosis.

## **COSTS**

Over 183,000 prescriptions for Hormone Replacement Therapy were dispensed under the General Medical Services (GMS) scheme in 1994 at a cost of almost £1 million.

### **Cost of Hormone Replacement Therapy for 28 Days Treatment**

Drug costs are based on data from GMS 1996.



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