UPDATE ON HORMONE REPLACEMENT THERAPY
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It is now five years since I wrote an article on hormone replacement therapy (HRT) for this journal. Although the rate of release of new preparations has slowed, there have been some very significant developments in these years.

SAFETY

Firstly, some of my confidence about the safety and efficacy of HRT was unfounded. Within a few months of the last article the Lancet published three studies comparing the risks of thromboembolic disease (TED) in HRT users and non-users. To our surprise it showed that TED was three times as common in HRT users as in non-users. The absolute size of this effect, however, was very small, with one extra case per 5000 users. Furthermore, this was a new user effect and after being established on HRT for a year there was no difference between users and non-users. It suggests that some women have a propensity to thrombosis that HRT brings out and certainly any woman who has been using HRT for some time without problems need not be concerned.

More importantly, a large prospective randomised double-blind study compared continuous combined HRT with placebo for secondary prevention of myocardial infarction. The patients were not typical HRT users as they were 60 to 80 years of age and had all had a previous coronary event. Follow-up was only for four years. In the first year there were more deaths in HRT users than the placebo group, although things levelled out and by the four-year point there was no difference between the two groups. The study showed the same three-fold increase in TED. It did not draw any conclusions about protection against osteoporosis or breast cancer but then it was not designed to have the power to answer these questions. The conclusion is that doctors should no longer persuade women at high risk of coronary heart disease to go on HRT, but equally it does show that if women wish to take HRT for symptomatic relief then a history of CHD is not a contraindication.

BREAST CANCER

The evidence relating to breast cancer remains observational and a further difficulty is that most of the large studies looking at the risk of breast cancer on HRT do not specify what sort of HRT was used. The studies that do specify tend to relate to women on unopposed oestrogen, reflecting practice in the United States some years ago rather than the way HRT is used now. The best guess is that the risk of breast cancer from taking HRT is the same as the increase in risk after a delayed natural menopause; that is, a woman has the same risk of breast cancer if she goes through the menopause at 50 and takes five years of HRT as if she goes through a natural menopause at 55 (Table 1).

<table>
<thead>
<tr>
<th>USE OF HRT</th>
<th>CASES PER THOUSAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>45</td>
</tr>
<tr>
<td>4-5 years</td>
<td>47</td>
</tr>
<tr>
<td>5-10 years</td>
<td>51</td>
</tr>
<tr>
<td>10-15 years</td>
<td>57</td>
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</tbody>
</table>

Table 1 Risk of breast cancer by age 70 per 1000 of 50-year-old women

Another way of putting the breast cancer risk of HRT into context is to tell patients that it is a smaller relative risk than that associated with obesity, excessive alcohol intake or delaying the first pregnancy to the age of 35.

A frequent concern for doctors is women with a family history of breast cancer. Familial cancers tend to be less well...
differentiated and, therefore, less likely to be stimulated by hormone treatment. It is probable that women with a family history of breast cancer get the same absolute rise in risk as other women, but starting from a higher base. For example, if a woman’s family history gives her a risk of breast cancer of 145 per thousand, using HRT for five years would only increase the risk to 147 per thousand. Clear information to the patient and good documentation in the notes is necessary in this situation.

NEW PREPARATIONS

There are some interesting new products, both of conventional HRT and of the class of drug known as “selective estrogen receptor modulators” or SERMs.

Continuous combined HRT

I remain concerned about the high number of women bleeding on these preparations well after the initial six months. I have never found any malignancy or even hyperplasia in such patients, but this symptom cannot be ignored and investigation is inconvenient for the women and consumes resources. In an attempt to decrease bleeding rates two preparations have gone to a 1mg estradiol dose, Kllovance and Femoston Conti. It is difficult to be certain how they compare with the 2mg dose for osteoprotection, since there is no dose-ranging study with fracture as an endpoint. Where the main reason for HRT use is symptom relief and the woman would not accept any bleeding they would be reasonable choices.

Transdermal oestrogen

The number of patche continue to increase, and there is now a wide range of dosages. Nuvelle TS is unusual in that it has a lower estrogen dose during the levonorgestrel phase, while Evorel Sequi and Conti use norethisterone transdermally. There is little clinical information about these systems, and they continue to be much dearer than oral preparations.

Oestrogel has now been joined by Sandrena estradiol gel. Sandrena requires a smaller application area. The main indication for them remains women more suited to transdermal therapy whose skin cannot tolerate being covered by a patch.

Vaginal therapy

Dienoestrol has been withdrawn. The most potent agent is now Premarin cream, which should not be used unopposed over the long term in a woman with a uterus. Ortho-Gynest cream is low strength and Ovestin higher strength oestriol, a less potent estrogen than oestradiol. Vagifem and Estring release very low doses of estradiol.

Progestogens

Apart from the developments in the progestogen patch mentioned above, the other new product is Crinone, 4% progesterone vaginal gel. An applicator is used to apply this on alternate days for 12 days monthly. It is a reasonable alternative for a woman who has side effects with oral or transdermal progestogen and is happy to use this route.

<table>
<thead>
<tr>
<th></th>
<th>Estrogen</th>
<th>Tazoxifen</th>
<th>Raloxifene</th>
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<tr>
<td>menopause symptoms</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>breast safety</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>endometrial safety</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>bone benefit</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>heart benefit</td>
<td>?</td>
<td>?</td>
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</table>

Table 2 Effects of estrogen and SERMs

SERMs

Tamoxifen was first developed as a contraceptive because it prevented estrogen-induced growth of the rat uterus. It failed as a contraceptive and was then found to be a treatment for breast cancer. Clomiphene stimulates ovulation by blocking the pituitary estrogen receptor. These agents are called first generation SERMs.

Raloxifene is the first second generation SERM to become available. The MORE (multiple outcomes of raloxifene) study enrolled 7705 osteoporotic women and randomised them to placebo or raloxifene at 60 or 120 mg. There was an increase in bone mineral density and a reduction in vertebral fractures on raloxifene. There was a reduction in nonvertebral fractures which did not reach statistical significance. The cardiovascular effects will be clarified by the raloxifene use for the heart (RUTH) study, but the effects on lipids are favourable. There were no adverse endometrial effects. The breast data are also promising and are being studied in the STAR (study of tamoxifen and raloxifene) trial. The impact on TED was the same as HRT, ie a threefold increase. It was of no benefit for menopausal symptoms. It is not a contraceptive and might be teratogenic. The licence is for post-menopausal woman with, or at high risk of, osteoporosis.

SUMMARY

We have many useful drugs at our disposal. HRT has not been shown to have such beneficial effects as enthusiasts hoped, nor are the risks as high as pessimists feared. Instead it has a place alongside statins, bisphosphonates, raloxifene and lifestyle advice to improve the health of postmenopausal women.

BIBLIOGRAPHY


**Balance by Kliovance**

**High compliance**

**Low dose, period-free HRT**

**KLIOVANCE®**

1mg ESTRADIOL, 0.5mg NORETHISTEROONE ACETATE

**Kliovance - where less is more**

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**Abbreviated Prescribing Information.**

**Kliovance®, Estradiol, Noriestosterone Acetate.**

**Presentation:** Calendar pack containing 28 white tablets each containing 1mg estradiol and 0.5mg norethisterone acetate. Uses: Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in women who are more than one year past the menopause. Prevention of osteoporosis in postmenopausal women.

**Dose and Administration:** One tablet daily without interruption intended for women with an intact uterus. Consider switch to higher dose if insufficient symptom relief after three months. For prevention of osteoporosis decreasing effect on bone mass in individuals already treated may be taken into account.

**Contra-indications:** Pregnancy or suspected pregnancy, lactation, breast cancer (including past history) and estrogen-dependent tumours. Undiagnosed vaginal bleeding. Active or recent thromboembolic processes. Acute or chronic liver disease or history as long as liver function tests have failed to return to normal. Hypersensitivity to ingredients.

**Precautions:** Take personal and family medical history prior to initiation or reinitiation of HRT. Periodic check-ups are recommended. Reproductive health benefit ratio periodically during treatment. Patients with a history of estrogen-dependent tumours, leukaemia, endometriosis, endometrial hyperplasia, fibrocystic disease of breast, a history of thromboembolic disorder or presence of risk factors, hypertension, diabetes mellitus with vascular involvement, liver disorders, cholelithiasis, migraine or severe headache should be monitored carefully as HRT may exacerbate these conditions. Edema may cause fluid retention, monitor patients with cardiac or renal dysfunction. In patients with end stage renal disease keep in mind possibility of increasing cardiovascular levels of active components. If asthmatic, epilepsy or diabetes are aggravated reconsider HRT. Epidemiological studies suggest that HRT is associated with a higher relative risk of developing VTE. Consider risks and benefits in patients with recognised risk factors for VTE. Risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. Give appropriate prophylactic measures to prevent VTE following surgery. Consider temporarily stopping HRT for four to six weeks prior to surgery if prolonged immobilisation expected. Discontinue HRT if VTE develops. Use of HRT for more than 5 years associated with increase in risk of breast cancer. The risk increases with duration of treatment and decreases after treatment stopped. Carry out regular breast examination and where appropriate mammography. Monitor breast status of patients with breast nodules, fibrocystic disease or family history of breast cancer. Increased risk of gall stones in susceptible individuals. Increased risk of developing SEI reported. Breakthrough bleeding and spotting often occur during first few months of treatment. Discontinue Kliovance if unacceptable. Bleeding after a period of amenorrhoea or which persists after stopping treatment requires investigation. Side Effects: Most frequently reported adverse events in clinical trials was breast tenderness, mainly during initial months of treatment. Other adverse events reported in clinical trials were: headache, vaginal bleeding, abdominal pain, nausea, haemorrhoids, breast enlargement, increase in size of existing fibroma, skin rash and pruritus, iron deficiency anaemia, VTE and oedema. Other side effects which have been associated with estrogen/progestogens: Energy, dyspepsia, vomiting, bloating, loss of taste or smell, photophobia, migraine, dizziness, vaginal candidiasis, increase in breast size, oedema, leg swelling, weight changes, depression, VTE and anaemia. Exceptional cases of thrombocytopenia, megaloblastic anaemia, G6PD deficiency and thromboembolic events has been reported. PL Number: PL 012332/0125. PL Holder: Novo Nordisk Ltd, Broadhall Way, Hertfordshire.

Legal Category: POM. Basic NHS Price: £9.56 for 28 days treatment. Date of Preparations: March 2001. Full prescribing information can be obtained from Novo Nordisk Limited. NovoCare Customer Care Centre: 0845 500 5055. Local rates apply. Calls may be monitored for training purposes. Information available on our website at: www.novonordisk.co.uk K1/01/19