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).

USE OF HRT	CASES PER THOUSAND
none	45
4-5 years	47
5-10 years	51
10-15 years	57

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

Fig 1. Kaplan-Meier estimates of the cumulative incidence of primary coronary heart disease (CHD) events (left) and to its constituents: nonfatal myocardial infarction (MI) (centre) and CHD death (right). The number of women observed at each year of follow-up and still free of an event are provided in parentheses, and the curves become fainter when this number drops below half of the cohort. Log rank P values are .91 for primary CHD events, .46 for nonfatal MI, and .23 for CHD death.

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, Kliovance 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 patches continues 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.

	Estrogen	Tamoxifen	Raloxifene
menopause symptoms	+	-	-
breast safety	-	+	+
endometrial safety	-	-	+
bone benefit	+	+	+
heart benefit	?	?	?

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

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women JAMA 1998;280(7):605-613

Herrington D, Reboussin D, Brosnihan B, Sharp P, Shumaker S, Snyder T, Furberg C *et al* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. New Engl J Med 2000;343(8):522-529

Abbreviated Prescribing Information.**Kliovance®. Estradiol, Norethisterone****Acetate. Presentation:** Calendar dial 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. **Dosage****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 dose-related effect on bone mass and

individual tolerability must 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 before

initiation or reinstitution of HRT. Periodic checkups

are recommended. Reappraise risk-benefit ratio

periodically during treatment. Patients with: a

history of estrogen-dependent tumours; leiomyoma,

endometriosis, endometrial hyperplasia, fibrocystic

disease of breast; a history of thromboembolic

disorders or presence of risk factors; hypertension;

diabetes mellitus with vascular involvement; liver

disorders; cholelithiasis; otosclerosis; migraine or

severe headache; should be monitored carefully as

HRT may exacerbate these conditions. Estrogens may

cause fluid retention, monitor patients with cardiac or

renal dysfunction. In patients with end stage renal

disease keep in mind possibility of increasing

circulatory levels of active components. If asthma,

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 scrupulous

attention to 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

SLE reported. Breakthrough bleeding and spotting

often occur during first few months of treatment;

discontinue Kliovance if unacceptable. Bleeding after

a period of amenorrhea or which persists after

stopping treatment requires investigation. **Side****Effects:** Most frequently reported adverse event 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, flatulence, breast

enlargement, increase in size of uterine fibroids,

skin rash and pruritus, insomnia, depression, VTE

and oedema. Other side effects which have been

associated with estrogen-progestogen therapy:

dyspepsia, vomiting, bloating, loss of scalp hair,

hirsutism, migraine, dizziness, vaginal candidiasis,

increase in blood pressure, increase or decrease in

weight, changes in libido, leg cramps. Exceptional

cases of chloasma, erythema multiforme, erythema

nodosum and haemorrhagic eruption has been

reported. **PL Number:** PL 03132/0125. **PL****Holder:** Novo Nordisk Ltd, Broadfield Park, BrightonRoad, Crawley, West Sussex RH11 9RT. **Legal****Category:** POM. **Basic NHS Price:** £8.65 for28 days treatment. **Date of Preparation:**

March 2001. Full prescribing information can be

obtained from Novo Nordisk Limited. **NovoCare****Customer Care Centre:** 0845 600 5055.

Local rates apply. Calls may be monitored for

training purposes. Information available on our website at:

www.novonordisk.co.uk

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High compliance

Low dose

Low dose, period-free HRT KLIOVANCE®

1mg ESTRADIOL, 0.5mg NORETHISTERONE ACETATE

Kliovance - where less is more