Hormone replacement therapy for all? Universal prescription is desirable

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This is one in an occasional series of articles examining some of the difficult decisions that arise in medicine

At a recent European consensus development conference on the menopause (Montreux, Switzerland, September 1995) it was concluded that hormone replacement therapy improves the quality of life, increases collagen, reduces urinary symptoms, and improves cognitive function. Although hormone replacement therapy has become an everyday part of the lives of millions of women, there are three main reasons why many who would benefit do not take oestrogen supplementation.

Why some women reject therapy

MISCONCEPTION ABOUT THE MENOPAUSE

Some women believe that the menopause is a natural event and that taking medication (hormones) should be avoided. These women are wrong: oestrogen deficiency is the unnatural state. In developed countries the menopause occurs at around 51 years of age, although in women who have had a hysterectomy it may occur slightly earlier. During this century life expectancy has increased from 62 to 80 years.¹ Thus women now live more than one third of their lives after the menopause.

Premenopausal women are protected against cardiovascular disease by circulating oestrogen. This advantage is lost after the menopause. In the United States prescribing hormone replacement therapy is estimated to save the health budget \$60m a year.² Osteoporosis is common in elderly women and causes appreciable morbidity through fractures of the vertebrae, wrist, and neck of femur. These may not be seen for years after the menopause but early treatment could save a further \$10bn of the American health budget.

CANCER WORRY

Women are worried about the risk of cancer,³ particularly of the breast and endometrium. Several factors must be considered when assessing the association between hormone replacement therapy and cancer. The likelihood of strokes and ischaemic heart disease is around five times greater in terms of lifetime risk than endometrial and breast cancer.⁴ Long term treatment with a natural oestrogen halves the risk of ischaemic heart disease and gives a 60% reduction in osteoporotic fractures.^{5,6} Against this is the possibility of doubling the risk of endometrial cancer from unopposed oestrogen (which is rarely used systemically except in hysterectomised women) and a 1.1-1.3 relative risk of breast cancer.⁷⁻¹⁰ The possible increased incidence of cancer may be reduced by improved techniques of medical surveillance such as transvaginal ultrasound assessment of endometrial thickness and regular mammographic screening for women over 50. In addition, increasing evidence of significant differences in the breast cancers being identified by mammography indicates less risk of metastasis and lower grade cancers,^{11,12} suggesting that we are picking up a new population or detecting previously undetected disease.

INCONVENIENCE OF MENSTRUATION

Women do not like the return of monthly bleeds. This is the largest single cited reason why women either never start hormone replacement therapy or stop within the first three months.^{13,14} However, over the past 10 years much research has been invested in the

development of non-bleeding preparations such as tibolone and continuous combined oestrogen and progestogen regimens.^{15,16} Also within the past year the levonorgestrel intrauterine system has become available, which offers an alternative to oral progestogens by working at the appropriate site to maintain an atrophic endometrium.

Weight of evidence favours therapy

There is now a wide variety of preparations and routes of administration of oestrogen that allow local treatment for urogenital atrophic complaints—for example, patches, implants, and creams to avoid the first pass effect—and thereby reduce the dosage required and the side effects.

There is increasing evidence to suggest that hormone replacement therapy can be important in improving the quality of life by reducing urinary symptoms¹⁷ and improving psychological wellbeing.¹⁸ Recent publications also suggest a protective effect against Alzheimer's disease,^{19,20} which is leading to increasing interest in the role of hormone replacement therapy in preventing this condition through increasing cerebral blood flow, antidepressive effects, and neuronal stimulation. The weight of evidence must now be in favour of using hormone replacement therapy as widely as possible.

Often, however, despite preconceived ideas a woman seeks advice from her doctor, and it is interesting to note that in 1994 only 64% of gynaecologists and 56% of general practitioners thought that all women should be offered hormone replacement therapy.²¹ Perhaps now many would change their opinion in the light of increased awareness of the benefits and realisation that many of the earlier fears of cancer are unfounded. Current health trends emphasise the importance of improved quality of life. This should include the widespread use of hormone replacement therapy to enable women to remain healthy into old age.

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Not for everybody

H S Jacobs

In thinking about this debate I suggest two broad themes to consider before turning to precise clinically based contraindications. The first is that if hormone replacement therapy really is so good for you why do so few women take it? The figures may be changing slightly, but at present in the United Kingdom fewer than 15% of eligible women are thought to start the treatment and fewer than 5% persist with it for more than a couple of years. When patients reject our advice doctors tend to lapse into omnipotence and berate them for their ignorance or fecklessness. It is therefore of great interest that Isaacs *et al* recently published the results of a study of 1200 women doctors aged between 40 and 60: they found that 40% of those who were postmenopausal had never even tried hormone replacement therapy.¹ Is it that our medical colleagues are feckless and ignorant, or is there something they know that Toozs-Hobson and Cardozo and I don't?

Paucity of solid data

The second consideration is the very real lack of solid data on which to base decisions about recommending universal prescription of hormone replacement therapy. It would be wonderful to have to hand the results of at least one randomised prospective trial that evaluated the outcome of treatment in terms of clinical events such as rates of fracture or heart attacks. All we have available is a comparison of the state of health of groups of women who chose to take hormone replacement therapy with that of groups of women who chose not to. Matching the groups appropriately is an obvious problem. Quite apart from questions of whether the control group is obtained from a hospital based population or the community or is matched for age, social class, compliance with advice related to the promotion of health, etc, women who decide to take hormone replacement therapy often have attitudes and behaviour with respect to healthy living that are quite different from those of women who decide against treatment.

Barrett-Connor described how, as a group, women who take hormone replacement therapy eat healthier diets, take more exercise, and have more contact with their doctors than do other women.² Cauley *et al* calculated that, before treatment, women over the age of 65 who subsequently chose to take hormone replacement therapy had a lower risk of coronary disease and possibly breast cancer but a greater risk of hip fractures than those who chose not to take it.³ Though consistency is now emerging in reports of the benefits of oestrogen treatment, the effects of these and other known and unknown biases certainly erode confidence in the magnitude of the benefits claimed. As an example, a review of published work led one group of epidemiologists to conclude that hormone replacement therapy prevents about 50% of heart attacks in postmenopausal women⁴; review of the same work suggested to another group that the improvement was about half that.⁵ If we cannot measure the size of the benefits accurately is there rea-

son to imagine we can balance them accurately against the risks of treatment?

The cancer question

Specific contraindications to hormone replacement therapy are few, though adverse reactions—particularly to the progestogen component—are what usually limit compliance. Clearly, therefore, before recommending hormone treatment for all it will be necessary for the pharmaceutical industry to produce more acceptable preparations. But I find that what finally limits the acceptability of postmenopausal hormone replacement therapy is the fear that treatment with hormones causes cancer. Is this fear reasonable? I think we all accept that when oestrogens are "opposed" by cotreatment with progestogens the fivefold to eightfold increased risk of endometrial cancer associated with treatment with oestrogen alone falls to background levels or below⁶ (though it is worth noting that in the United States—which has the largest and longest experience of oestrogen treatment—a combined preparation licensed for postmenopausal hormone replacement therapy has become available only in the past 18 months).

The position with regard to breast cancer is not, however, so simple. In 1992 Loeffler and I reviewed a substantial body of original studies plus five meta-analyses indicating that after 10 years or more of hormone replacement therapy the relative risk of breast cancer lay between 1.1 and 1.3.⁷ There is evidence that the risk increases with the dose and duration of treatment and none that it is reduced by using combined preparations rather than unopposed oestrogen.⁸ Many postmenopausal women know someone who has or has had the disease, so their fear should not be lightly dismissed. Moreover, the use of high dose (oestrogen implant) and long term (more than 10 years) treatment should be undertaken only after full and careful discussion of these risks.

Contraindications to postmenopausal hormone replacement therapy

- Undiagnosed vaginal bleeding
- History of endometrial atypical hyperplasia or cancer
- History of breast cancer?
- Hypertriglyceridaemia
- Gall stones
- Specific disturbances of blood clotting—for example, protein C deficiency, possibly antithrombin III deficiency
- Vague psychiatric disturbances, particularly unrecognised depression

The most important contraindication to treatment is when the patient has nothing to gain.

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