

MENOPAUSE AND HORMONE REPLACEMENT THERAPY

How does a woman decide? What should a doctor advise?



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Professor Davey trained at St Mary's Hospital and the Postgraduate Medical School, London. He was Professor of Obstetrics and Gynaecology at the University of Cape Town from 1965 to 1990 and was then in private practice for 12 years. In 1967 he started the Mature Woman's Clinic at Grootte Schuur Hospital with Dr Wulf Utian. He is still an active member of the clinic and has continued his keen interest in the menopause and women's health.

The menopause is a normal, natural biological process that is often associated with vasomotor symptoms and may be associated with long-term changes such as bone loss.

Vasomotor symptoms such as hot flushes occur in about three-quarters of all women and are nearly always completely relieved by HRT, which is by far the most effective treatment. The relief of menopausal symptoms, including sleep disturbances and mood changes, can transform the quality of life. Long-term changes such as bone loss may start at the menopause but only manifest much later in life as a catastrophic osteoporotic fracture. Many conditions, including osteoporosis and fractures, increase in incidence with advancing age and may be prevented or treated by appropriate therapy (that may include HRT), as well as by dietary and lifestyle modifications.

The menopause is an ideal time to take stock and undertake a comprehensive health review with the aim of happy and successful ageing.

MAKING DECISIONS ABOUT HRT

Decisions about hormone replacement therapy (HRT) and all health issues at and after the menopause always rest with each woman after consultation with her medical adviser. Most women have some fears and uncertainties about the menopause and the risks and benefits of HRT. These fears and uncertainties have been greatly increased since the publication of the results of the Women's Health Initiative (WHI) clinical trials and the subsequent publicity in the lay media. In May 2002 the oestrogen plus progestin arm of the WHI trials was terminated early, primarily because of a significantly increased risk of breast cancer.¹ In February 2004 the oestrogen-only arm was also terminated early, primarily because of an increased risk of stroke, although the risk of breast cancer was not increased (and was probably decreased²).

HRT has very substantial benefits, including the relief of menopausal symptoms such as hot flushes as well as a reduction in the risk of fracture and of colorectal cancer. Some understanding of the nature and extent of both the risks and the benefits of HRT is essential in any decision-making. Professor Speroff has stressed that decision-making regarding the menopause and HRT requires an individual assessment of each woman's symptoms, physical state, medical and family history and personal wishes and goals. Any advice or decision requires an individual 'medical judgment' based on the practitioner's accumulated knowledge and understanding acquired through education, experience and appraisal of the medical literature. A medical judgement is not made on any one clinical finding or any single scientific study but is based on the overall assessment of each woman and the summation of the practitioner's understanding and experience. A judgement may change over time as a woman's needs change and as new knowledge and understanding are acquired, and medical judgements always require periodic review.

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CALCULATING RISKS AND BENEFITS

The risk of two conditions — breast cancer and cardiovascular disease — has come to dominate decision-making about HRT. Both conditions have many aetiological factors and both increase in incidence with advancing age. The results of the landmark WHI trials of oestrogen plus progestin (EPT)¹ and of oestrogen-only (ET)² in postmenopausal women on the risk of breast cancer may be used to put the risks and benefits of HRT in perspective. Risks (and benefits) are commonly expressed statistically as a *relative risk* (RR), and less often as an *absolute risk* and an *attributable risk*. In the EPT arm of the WHI trial the RR for breast cancer associated with an average of 5.2 years of treatment was 1.24 and indicated a statistically significant 24% increase in the ratio of the number of women who developed breast cancer in the treated group compared with the placebo group. The absolute risk of breast cancer in the women who received EPT averaged 3.75/1 000 women/year and in the women who received placebo averaged 2.95/1 000 women/year and the attributable risk was 0.8/1 000 women/year. Only approximately 1 case of breast cancer per 1 000 women per year was attributable to HRT. Attributable risks may be so small as not to be of clinical significance, especially in relation to other risk factors. The increased risk of breast cancer associated with oestrogen and progestin in the WHI trial is in fact about the same as, or

less than, the increased risk associated with a family history of breast cancer,³ obesity⁴ or alcohol use.⁵

In making decisions and medical judgements about the use of HRT, it is necessary to take into account the absolute and attributable, as well as the relative risks and benefits. In evaluating the significance of risks the associated morbidity and mortality are of great importance. Thus although the incidence of breast cancer is increased with EPT, the mortality is not increased and is probably decreased.⁶ This may be due to earlier detection but also because the cancers associated with HRT tend to be less advanced.⁷ The hormone composition of the HRT may also be of critical importance. In the ET arm of the WHI trial the incidence of invasive breast cancer in women given ET, compared with the placebo group, was in fact decreased by 23% and the RR of 0.6 'narrowly missed statistical significance'. There is increasing evidence that the risk of breast cancer with EPT is mainly due to the addition of a progestin.⁸

WHEN IS AN INCREASE OR A DECREASE IN RISK SIGNIFICANT?

The decision whether a risk or benefit is statistically significant is often crucial, particularly when conclusions are drawn and conveyed to the lay public. Statistical significance is arbitrary as it depends upon the degree of probability or confidence set. By convention, a probability of $p < 0.05$ and confidence limits of 95% are regarded as statistically significant. If other degrees of probability or confidence are applied, such as $p < 0.1$ or $p < 0.01$ and 90% or 99% confidence limits, entirely different conclusions may be drawn as to what is statistically significant. The statistical results of clinical trials with multiple outcomes, such as the WHI trial, may also require to be adjusted for multiple significance testing. When the Bonferroni correction was applied in the EPT arm only the increased incidence of thromboembolic disease, and the decreased inci-

dence of total fractures, remained statistically significant. When the same correction was applied to the ET arm none of the findings were significant.

All clinical trials and statistical analyses require interpretation and simplistic, clear-cut conclusions can rarely be drawn as is often done in the lay media. The main criticism of the WHI trials is that the subjects were mainly older postmenopausal women (mean age 63.2 years and 63.6 years), and that the findings do not necessarily apply to younger women (age 50 - 60 years) who are most frequently given HRT. The absolute risks of most chronic diseases double with each decade increase in age and a study reporting a few additional cases of a disease per 10 000 women per year in an older population may not be applicable and relevant to a younger population where the prevalence of the disease is very much less. The decision on whether a finding that is statistically significant is also clinically significant and relevant requires a value judgement in each case.

BALANCING RISKS AND BENEFITS AND ASSESSING THE QUALITY OF LIFE

Many attempts have been made to balance the risks and benefits of HRT and to derive global summary indices of risk and benefits and scores of quality of life. For women with hot flashes, night sweats and sleep disturbances, the overwhelming and immediate need is for the relief of symptoms and this frequently outweighs consideration of the remote long-term risks and benefits of HRT. Relief of vasomotor symptoms often greatly improves, if not transforms, the quality of life and well-being of many women and has to be taken into account in balancing the benefits and risks of HRT. In the WHI trials women with vasomotor symptoms were generally excluded and the global indices were based on the balance of the long-term risks and benefits of major diseases (Tables I and II are from the initial publications of the WHI trials^{1,2}). In the EPT arm it was concluded that the increased risks of breast

Table I. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women¹

Outcome	Hazard ratio	Nominal 95% CI	Absolute risk CEE + MPA*	Absolute risk placebo*	Attributable risk CEE + MPA*
CHD	1.29	1.02 - 1.63†	3.70	2.90	0.77 more
Stroke	1.41	1.07 - 1.85†	2.8	2.02	0.85 more
VTE	2.13	1.39 - 3.25†	3.39	1.59	1.80 more
Breast cancer	1.26	1.00 - 1.59†	3.75	2.95	0.80 more
Colorectal cancer	0.63	0.43 - 0.92†	1.02	1.59	0.57 less
Total fracture	0.76	0.69 - 0.85†	15.43	18.70	3.27 less
Global index‡	1.15	1.03 - 1.28†	16.98	14.79	2.19 more

CI = confidence interval; CEE = conjugated equine oestrogen; MPA = medroxyprogesterone acetate; CHD = coronary heart disease, VTE = venous thromboembolic disease.

*Number per 1 000 women per year (mean duration of trial 5.2 years)

†Statistically significant at the 95% level unadjusted CI

‡Global index: balance of first events among CHD, stroke, pulmonary embolus, breast cancer, colorectal cancer, hip fracture or death from other cause.

Table II. Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy²

Outcome	Hazard ratio	Nominal 95% CI	Absolute risk CEE*	Absolute risk placebo*	Attributable risk CEE*
CHD	0.91	0.75 - 1.12	4.90	5.39	0.49 less
Stroke	1.39	1.10 - 1.77†	4.38	3.19	1.19 more
VTE	1.33	0.99 - 1.79	2.80	2.11	0.69 more
Breast cancer	0.77	0.59 - 1.01	2.60	3.36	0.76 less
Colorectal cancer	1.08	0.75 - 1.55	1.69	1.57	0.12 more
Total fracture	0.70	0.63 - 0.79†	13.93	19.61	5.68 less
Global index ‡	1.01	0.91 - 1.12	19.16	19.10	0.06 more

CI = confidence interval; CEE = conjugated equine oestrogen; CHD = coronary heart disease; VTE = venous thrombembolic disease.

*Number per 1 000 women per year (mean duration of trial 6.8 years)

†Statistically significant at 95% level unadjusted CI

‡Global Index: balance of first events among, CHD, stroke, pulmonary embolus, breast cancer, colorectal cancer, hip fracture or death from other cause.

cancer, coronary heart disease (CHD), pulmonary embolus and stroke outweighed the reduced risks of colorectal cancer and hip fracture. In the ET arm the risk of stroke was increased but the cardiovascular disease and colorectal cancer were unchanged and there was a significant reduction in the incidence of total fractures, and possibly also of breast cancer.

It was concluded that the incidence of diseases in the treated and placebo groups was equivalent and that ET conveyed no overall benefit. These conclusions however are only applicable to the group of mainly older postmenopausal women in the WHI trial and not necessarily to younger postmenopausal women. The risks of EPT and ET in healthy younger post-

menopausal women are extremely small and have to be balanced against the major benefit of the relief of menopausal symptoms and improvement in quality of life, as well as other long-term benefits of HRT.

Opinion is changing about the use of HRT, and the South African Menopause Society has recently pub-

lished a revised consensus statement on the risks and benefits of menopausal hormone therapy (SAMJ 2004; **94**: 75-77).⁹ The North American Menopause Society has also recently updated its recommendations on oestrogen and progestogen in peri- and postmenopausal women with some important revisions, including:¹⁰

- No ET or EPT regimens should be used for the primary or secondary prevention of CHD, but the role of both ET and EPT in primary prevention of CHD in younger women remains unclear, especially in those starting early.
- The risk of breast cancer probably increases with EPT use but not ET use. ET and EPT can still be considered for reducing osteoporosis risk.
- The use of ET/EPT should be limited to the lowest effective dose but no limit need be placed on duration of ET/EPT provided it is monitored regularly and is consistent with treatment goals, benefits and risks for the individual woman.
- No single trial should be used to set public health policy. The practice of medicine must ultimately be based on the interpretations of the entire body of evidence currently available, given that there will never be adequate clinical trials to cover all populations, eventualities and regimens.

The main purpose of HRT is the relief of menopausal symptoms, and the following are some guidelines that may assist the practitioner and the woman he/she advises:

- **Age.** Young healthy peri- and postmenopausal women (under 60) are much more likely than relatively older women to experience distressing menopausal symptoms and are at a very small, if not a clinically insignificant, risk of breast cancer, CHD, stroke and thromboembolic disease. In women in the middle years (60 - 70) there is a balance between the benefits of the relief of symptoms (and the prevention of osteoporosis) and the long-term risks, including an increase in the

incidence of breast cancer. In women over 70 years the increased risks, including an increased risk of stroke and dementia, outweigh the benefits for most women. The consensus of opinion is that women who have had a premature ovarian failure or oophorectomy (under 45) should receive long-term therapy, irrespective of whether or not they have any menopausal symptoms, for the prevention of osteoporosis and of other possible long-term conditions including cardiovascular disease.

- **Severity of symptoms.** Menopausal symptoms including hot flushes, sleep disturbances and mood changes vary from the mild and occasional to the severe and incapacitating. HRT provides the only completely effective relief. Other treatments in general only reduce the incidence of menopausal symptoms and are only effective in a proportion of women. The more severe the symptoms and the greater the impact on the quality of life, the greater is their weight in the balance of benefits and risks.
- **Medical status and medical history.** In women with uncontrolled hypertension or with a history of breast cancer, myocardial infarction, stroke and thromboembolic disease HRT carries a much greater risk than in healthy postmenopausal women and HRT is, in general, contraindicated. A family history of breast cancer is not a contraindication to HRT but is an indication for closer breast surveillance. A personal or family history of thromboembolic disease is an indication for tests to exclude hereditary thrombophilias. The screening for common medical and gynaecological conditions and their investigation and treatment is an integral part of care.

CONCLUSION

Much is made of the risks of HRT, and HRT is often regarded as controversial. In practice, after assessment, explana-

tion and discussion most women come to a decision quite easily. The challenge for the doctor is to make a correct and balanced medical judgement and to convey this in a way appropriate to each woman. By relieving menopausal symptoms and enabling women to live full and active lives without embarrassment or distress, HRT can make a major contribution to the quality of life and the well-being of women at and after the menopause.

References available on request.

IN A NUTSHELL

The menopause is an ideal time to make a comprehensive health review.

Decisions about HRT rest with each woman after consultation with her doctor.

Decision-making requires an individual 'medical judgement'.

The absolute and attributable risks and benefits of HRT as well as the relative risks must be considered.

Statistical significance does not always imply clinical significance.

Conclusions from relatively older groups of women in WHI trials do not necessarily apply to younger postmenopausal women.

Younger postmenopausal women have more distressing menopausal symptoms and much lower absolute risks.

For many women the immediate need for relief of menopausal symptoms outweighs consideration of both long-term risks and benefits.

Age, severity of symptoms, medical status and history are key factors in decision-making.

HRT is the most effective treatment for vasomotor symptoms and enables many women to live full and active lives without embarrassment or distress.