HRT and heart disease

Death from coronary artery disease in premenopausal women is relatively infrequent, compared to men of similar age. After the menopause the incidence of cardiovascular disease rises rapidly to become the commonest cause of death. The question which multiple trials have addressed recently is whether hormone replacement therapy (HRT) can reduce the postmenopausal risk of cardiovascular disease. An appraisal of these trials is particularly important now that recent analyses have attempted to quantify the improvement in survival compared to other treatments for ischaemic heart disease.

Revascularisation with either percutaneous transluminal coronary angioplasty or coronary artery bypass surgery can be expected to improve the relief of angina, but their effects on survival are less spectacular than is suggested by the instant relief of symptoms. A recent meta-analysis of survival data following bypass surgery suggests that only a minority of patients undergoing operation have a substantial increase in life expectancy. Moreover, these observations were confined mainly to men; women probably benefit less than men, possibly because they have physically smaller coronary arteries which are technically more difficult to revascularise fully, and because they tend to present with symptoms at an older age. However, such bias against women may be more than compensated for by the potential benefits of HRT.

There is persuasive evidence from large cohort studies that postmenopausal oestrogen replacement therapy protects against cardiac disease. The largest observational study is the Nurses' Health Study, carried out in the USA during 1980–90. This study followed 48 000 women for over a third of a million woman-years. The risk of heart disease was reduced by almost 50% in those women receiving oestrogen HRT during the 10 years of the study. The benefit was even larger in women with established coronary disease, with 80% lower mortality in those who had used oestrogen.

While the rewards appear prodigious, close examination of the methodology of these observational studies has revealed important variables which may confound the apparent power of the proposed benefits. Firstly, during the 1980s, the period covered by the study, it was customary to withhold HRT from women at higher risk of cardiovascular disease. This was because HRT was considered to be a risk factor for thrombosis and hypertension. Moreover, HRT tended to be prescribed to women of higher social class, with less obesity, hypertension, diabetes and hyperlipidaemia, and correspondingly higher exercise and social alcohol intake. Therefore, the women who took HRT were already a more healthy, lower risk group than their controls. This bias in the cohort studies would select healthier women to receive HRT. It is also likely, although unproven, that US physicians avoided HRT in patients whom they suspected to have breast of ovarian disease, further loading the statistics in favour of the 'healthy cohort'. Hence, the apparently large benefits of HRT from the published studies may relate, at least in part, to baseline differences between the two cohorts.

The most serious drawback of HRT is the possibility of developing breast cancer, a risk which appears to rise with prolonged HRT usage. Addition of a progestrone to oestrogen (necessary to protect endometrial tissue from oestrogen in women with an intact uterus) has not been shown to affect this to a great extent. The risk of breast cancer rises when treatment is sustained beyond five years, with increases of between 50 and 70%. Yet the lifetime risk of breast cancer for a 50-year-old woman is about 8%, while the lifetime risk of coronary heart disease is about 45%. So are the favourable effects of oestrogens on the cardiovascular system worth the increased risk of breast cancer of between 12–15%? Can the individual balance the cardiovascular benefits of HRT against the increased risk of breast cancer? These are evocative arguments, but are speculations which are as yet difficult to quantitate. The evidence for HRT and development of breast and ovarian disease will come from randomised, controlled trials.

There are two groups of randomised trials which will determine the long-term future of HRT. Large, primary prevention trials in healthy women are already underway, co-ordinated by the Medical Research Council in the UK, and the National Institute of Health in the USA. These trials will recruit 25–50 000 women and follow-up will continue over 8–12 years. There are also smaller, secondary prevention trials of HRT in women with existing coronary heart disease. These trials should begin to report in 1998. These trials will take into account not only all-cause mortality but will also evaluate morbidity.

Until then, what should physicians advise? For women with established coronary heart disease or women who are at increased risk of coronary disease, substantial benefit from HRT is likely. This, at least, is the view of the American College of Physicians and makes good sense. This includes women with ischaemic heart disease experiencing menopausal symptoms, in whom HRT is now no longer contraindicated. A wider recommendation for HRT as primary prevention of coronary heart disease in healthy women cannot yet be given; but women and their physicians who wish a short-term (say five years) course following menopause to improve well being and offset osteoporosis should not be deterred. By then there will be more data to base decisions about therapy into the next century.

ADRIAN J B BRADY
Department of Medical Cardiology,
Glasgow Royal Infirmary,
Glasgow G4 0SF, UK

JOHN B WARREN
Department of Clinical Pharmacology,
UMDS St Thomas' Hospital,
London SE1 7EH, UK

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A. J. Brady and J. B. Warren

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