Oestrogens and cardiovascular disease

Postmenopausal oestrogens seem to reduce coronary heart disease

The low rates of coronary heart disease in premenopausal women were one justification for an early randomised trial of exogenous oestrogens in the secondary prevention of coronary heart disease in men. The trial was abandoned because the treatment caused more coronary disease. The deleterious effect of oral contraceptives on mortality and morbidity from cardiovascular disease has been confirmed; the attributable risk is greater in smokers and older women. These findings refer, however, to older preparations and to Western populations with high rates of cardiovascular disease. The risks associated with modern oral contraceptives seem to be lower and are under investigation.

The cardiovascular risks of oral contraceptives are related to both the oestrogen and the progestogen dose through various mechanisms. The adverse effect of progestogens on high density lipoprotein cholesterol concentrations seems to be an important pathway for increasing the risk of coronary heart disease, and the venous thromboembolic risks are related to the oestrogen dose.

Because of the effects of oral contraceptives researchers initially expected that oestrogens given after the menopause would increase mortality from cardiovascular disease. Because oestrogens are used so widely after the menopause, especially among American women, it is important that their effects should be clarified—even a small effect would be of major importance to public health. Although published reports on the cardiovascular effects of postmenopausal oestrogens have been confusing, the recent publication of several prospective studies has clarified matters.

The Framingham study found an increase of half in the risk of cardiovascular morbidity in users compared with non-users but no increase in the total mortality. This study looked at a cohort of 1234 postmenopausal women, a quarter of whom had used conjugated equine oestrogens between 1962 and 1972. In contrast, the nurses' health study of 32317 postmenopausal women studied in the late 1970s found an appreciable protective effect of postmenopausal oestrogens on coronary heart disease; just over half of the nurses had used oestrogens. The discrepancy between these two studies is probably explained by their different methods: a more rigorous reanalysis of the Framingham data, with harder end points and a modified definition of oestrogen use, found that oestrogens used after the menopause in women aged 50-59 protected against cardiovascular disease; an adverse effect was found in only a few aged 60-69.

A well executed study of deaths in a cohort of white women participating in the lipid research clinics prevalence study and seen initially between 1972 and 1976 showed a highly protective effect of non-contraceptive oestrogens on mortality from cardiovascular disease. The effect seemed to be mediated through an increase in high density lipoprotein concentrations; it seems unlikely to have been caused by a selection bias for oestrogen use—that is, women at low cardiovascular risk preferentially using oestrogens. The Walnut Creek prospective study found that postmenopausal oestrogens have a protective effect on mortality from all causes, including violent death, which suggests a selection bias. The prospective study with the largest number of hard end points was conducted in a Californian retirement community, and it too found that oestrogens reduced deaths from acute myocardial infarction. Postmenopausal oestrogens also seem to eliminate the increased risk of coronary heart disease in women who have had bilateral oophorectomy.

Thus the results from all community based prospective studies, except perhaps the Framingham study, show that postmenopausal oestrogens offer substantial protection against the risk of cardiovascular disease. Most of the community based case-control studies have also found a protective effect. All these prospective studies, however, have been conducted in the United States. Only one pilot case-control study has been reported from Britain, and
one other is in progress.15 All the studies have examined unopposed conjugated equine oestrogens rather than oestrogens cycled with progestogens, the regimen recommended to reduce the risks of endometrial cancer caused by unopposed oestrogens.16 The beneficial cardiovascular effects shown for unopposed oestrogens do not necessarily apply to women using modern combination treatment, which may not have such favourable effects on the lipid profile.17

It remains possible that oestrogen use reflects some other, unidentified factor that is the true cause of the low cardiovascular risk in users. Although this explanation seems unlikely,11 it may be conclusively ruled out only by randomised controlled trials.

If oestrogens do have a beneficial effect on cardiovascular disease this effect together with the beneficial effects on osteoporosis and menopausal symptoms will outweigh any remaining risk of endometrial cancer.18 But until the results of prospective studies, including randomised controlled trials, of modern combination treatment are available I think that it is premature to recommend using postmenopausal hormones to prevent cardiovascular disease.

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Complications of central venous cannulation

Trauma, infection, and thrombosis

Central venous cannulation is widely used in treating seriously ill patients and may give rise to serious complications. It is used to measure right atrial pressure when monitoring treatment and to give intravenous fluids, drugs, and long term parenteral nutrition.12 Most central venous catheters are inserted into the subclavian vein by the infraclavicular approach.13 Insertion into the internal jugular vein is less common but is sometimes used after an operation. The commonest early complications are related to local trauma and include pneumothorax, haemothorax, subcutaneous emphysema, subclavian haematoma and arterial damage, pleural effusion and hydromediastinum, brachial plexus injury, air embolism, and cardiac perforation.14

Infection usually occurs later in 7-16% of patients19 20 and in up to a third of those receiving hyperalimentation.9 The commonest pathogens are skin commensals, particularly staphylococci.20 Fungal infections also occur and may be associated with the cannula rather than with the intravenous fluid.13 14 Repeated flushing of the catheter with low dose amphotericin reduces the frequency of candida septicaemia.22 Sepsis of the catheter is usually primary, and the overall incidence of sepsis is not reduced by subcutaneous tunneling.9 15 The relation between the incidence of infection and how long the catheter remains inserted is unclear. Ryan et al noted no increase in the incidence of sepsis in catheters inserted for 30 days or more,9 but this has not been substantiated by others.16

Endocardial damage from indwelling catheters is well recognised at necropsy and includes aseptic valvular vegetations, subendocardial haemorrhage, sterile thrombus, and ulceration of valve leaflets.6 17 Infective endocarditis has been reported in 7% of cases at necropsy16 and most commonly affects the right heart, particularly the tricuspid valve.16 It seems to be more common with catheters in the pulmonary artery than with those in the right atrium. Left heart endocarditis is rare in patients without valvular disease,23 and giving antibiotics through a central vein to treat infective endocarditis is now common.

Central vein thrombosis is a serious complication and occurs in between 4% and 35% of patients.22 23 Thrombosis increases with the duration of catheterisation and is not related to the cardiac index.24 Other contributing factors include the nature of the line and its position, endocardial damage during insertion of the catheter, and concomitant infection. The most thrombogenic catheters are made from polyurethane and the least thrombogenic are from polyurethane coated with hydroxy. Silicone catheters are only slightly less thrombogenic than those made of polyurethane.24 Hoshal et al described a "fibrin sleeve" forming on polyethylene catheters and suggested that this was the initial step in the formation of a thrombus.25 Clots form mainly in the innominate veins, the superior vena cava, and the right atrium and are rare in the right ventricle26 27; clots in the right atrium are particularly common in neonates receiving parenteral nutrition.28 Thrombosis occurs more commonly with catheters in the pulmonary artery (33%) than with those in the right atrium (29%) and is more common during hyperalimentation.29 Connors et al noted that three fifths of patients with catheters had evidence at necropsy of either microscopic emboli (65%) or emboli in a major pulmonary artery (15%).29 Small mural thrombi commonly form in the great veins but are often adherent to the endothelium and so rarely produce important emboli.30 These thrombi develop within 48 hours after cannulation.30

The position of the catheter may reduce thrombosis and endothelial damage. Right atrial catheters are best placed high in the atrium or at the lower end of the superior vena cava. Catheters placed well within the body of the atrium may