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Hormone replacement therapy

Findings of women's health initiative trial need not alarm users

Observational studies have suggested a major health benefit of postmenopausal hormone replacement therapy, including reductions in coronary heart disease, osteoporotic fractures, and colorectal cancer. Such studies have also suggested an increased risk for breast cancer and possibly stroke. Critics have said that the benefits, but not the risks, may simply reflect a healthy user bias and have demanded randomised trials. The women's health initiative is a randomised trial of these health outcomes to assess risks and benefits of intervention strategies in a postmenopausal population. The trial has shown harm for cardiovascular diseases, including coronary heart disease (the primary outcome) and stroke, although it showed benefits for hip fractures and bowel cancer. The relative risks for invasive breast cancer, coronary heart disease, and stroke were increased, although the absolute risks were very small. The findings may not be the same for types of hormone replacement therapy other than those used in this trial, or for lower doses of the regimen that was used—a point that is acknowledged by the authors of the study.

One treatment arm of the trial included over 16 000 postmenopausal women who were taking continuous combined oestrogen-progestogen hormone replacement therapy, using conjugated equine oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily, tested against placebo.[1] This primary prevention study was due to run for 8.5 years but was halted at just over 5 years because the number of cases of breast cancer had reached a prespecified safety limit. For 10 000 women taking hormone replacement therapy each year, compared with those not taking it, there would be an additional eight cases of invasive breast cancer, seven heart attacks, eight strokes, and eight pulmonary embolisms. However, there would also be six fewer bowel cancers and five fewer hip fractures. Overall mortality was not increased with therapy.

Survival of the human species over two million years implies that female sex hormones by themselves are not dangerous to health. If harm is established, we must therefore examine the types of substitutes that we use and their means of delivery. The small increase in the number of patients with breast cancer accords with previous population studies,[2] as are the increases in venous thromboembolism and the decreases in fractures and in bowel cancer. Given the biological effects of oestrogen on the cardiovascular system, the lack of benefit on coronary heart disease is surprising—but these findings apply only to this particular hormone replacement therapy regimen, and other coronary heart disease studies of this hormone replacement therapy have not shown benefit.[3–5]

Hormone replacement therapy regimens using different oestrogens and progestogens, and different routes of administration, may be similar in their effects on the breast, bowel, and skeleton. But the metabolic effects of different regimens are clearly different,[6] and this is most likely to have an impact on their cardiovascular effects. Indeed, the women's health initiative trial also has an oestrogen-alone arm for women with hysterectomies, which has not been stopped. We need to see these findings to know whether the medroxyprogesterone acetate is causing the harm. It is most unhelpful that this point about different oestrogens and progestogens was not appreciated by the recent recommendations of the Committee for Safety of Medicines and the Medicines Control Agency,[7] which were inappropriate with respect to cardiovascular disease. Particularly for coronary heart disease, the dose (and possibly type) of oestrogen and the type of progestogen may be crucial. Similar studies using different types of hormone replacement therapy than the one used in this trial must be carried out.

Women who are currently taking continuous combined oestrogen-progestogen should not panic, as it is most unlikely to have caused considerable harm. Certainly the risk of breast cancer is not appreciably increased during the first four years, so women wishing to take this therapy for the short term relief of menopausal symptoms should be reassured. However, they need to discuss with their doctor whether they should shift to a different preparation, which could theoretically have a more beneficial effect on the cardiovascular system.

There is no right or wrong hormone replacement therapy to use in the short term, but in the light of the findings of this trial the use of hormone replacement therapy regimens containing conjugated oestrogens 0.625 mg together with medroxyprogesterone acetate (at any dose) should be avoided in the long term. The findings of this trial may not apply to lower doses of conjugated equine oestrogens, given with or without other progestogens. The long term effects of alternative hormone replacement therapy preparations have not yet been tested in large randomised trials, and this must become a research priority.

At present, long term hormone replacement therapy should be given only on an individual basis, depending on the needs and risk factors of the patient.

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Long term therapy could still be considered for prevention of osteoporosis, used as part of the management of women with particular cardiovascular risk factors, and used for better quality of life. We do not yet know the effects, if any, for the prevention of dementia, although preliminary evidence is encouraging. Women who are already taking long term hormone replacement therapy should be reviewed and counselled. If they need further treatment, consideration should be given to switching them to another form of hormone replacement therapy if they are taking a regimen of conjugated equine oestrogen and medroxyprogesterone acetate.

For women starting hormone replacement therapy, we continue to recommend that the starting dose of oestrogen is kept low in women over the age of 60. For example, this would be 1 mg for oral, or 50 μg for transdermal, oestradiol 17β—the 0.3 mg dose of conjugated equine oestrogens is not currently available in the United Kingdom. The risks and benefits of alternatives to hormone replacement therapy (such as tibolone and raloxifene) are still to be determined, but they are unlikely to be the same as the regimen used in the women's health initiative trial.

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An ethically defensible market in organs

A single buyer like the NHS is an answer

The American Medical Association has just voted to encourage studies that would determine whether financial incentives would increase the pool of donor organs from cadavers.[1] The association is only eight years behind a proposal that we made, outlining probably the only circumstances in which a market in donor organs could be achieved ethically and in a way that minimised the dangers of such a scheme. This is how an ethical market in live organs would work.

To meet legitimate ethical and regulatory concerns any such scheme must have built into it safeguards against wrongful exploitation and show concern for vulnerable people, as well as taking into account considerations of justice and equity. If all this can be done then a market in human body products will be shown to be, at the very least, not prima facie unethical.[2]

One way of attending to this need for prudent regulation would be to establish a monopsony, a situation where only one buyer exists for the products of several sellers.[3] The one legitimate purchaser in the marketplace would be required to take on responsibility for ensuring equitable distribution of all organs and tissues purchased. This would prevent the rich using their purchasing power to exploit the market at the expense of the poor. The monopsonist would also have other obligations, such as ensuring correct tissue typing to maximise histocompatibility and so minimise graft rejection, and screening for diseased or otherwise hazardous organs and tissues (for example, blood infected with HIV).

In the United Kingdom, the NHS would be ideally suited for this role. The NHS or a comparable monopsonistic purchaser would purchase live organs and tissues just as it does other goods such as dialysis machines or drugs. It would then make them available as needed on the basis of urgency or some other fair principle of distribution at no cost to the recipient.

In effect, the monopsonist is responsible for the running of the scheme. Should it also be permitted to set the prices of various organs and tissues that it is interested in purchasing? Leaving the pricing of organs to the judgment of the purchaser in a particular marketplace introduces the possibility of a conflict of interests. If the monopsonist was not only to act as purchaser, but also held responsibility for setting the price of what it purchases, it is not unlikely that it would attempt to set prices as low as possible so as to conserve its resources. This would, however, be counterbalanced by the need to provide sufficient incentives to attract would be organ vendors.

It might be thought that in a monopsonistic market there is no possibility for a pricing mechanism as in the free market. But the monopsonist is under pressure to purchase, this pressure resulting from the need for organs: if the purchaser is responsible for supplying patients with organs, and if demand from the public for

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