

Safety and risk in practice

Use of oestrogens to prevent cardiovascular disease in women

Ever since the use of oestrogen replacement therapy came into vogue forty years ago, it has been surrounded by doubt and controversy. The initial reason for this was that, while no-one could doubt that in some women lack of endogenous oestrogen led to problems at the time of the menopause and later, there was no satisfactory means of identifying in which women oestrogen supplementation was likely to be needed. Insofar as acute climacteric symptoms were concerned, these themselves indicated the potential users, but when one was considering the possibility of using oestrogens long-term to reduce the risk of complications ranging from osteoporosis to coronary heart disease one simply did not know in which individuals they were likely to be needed. Coupled with this was the increasing evidence that oestrogen use itself might induce new risks (such as that of endometrial carcinoma) sufficient to outweigh any uncertain prophylactic claims. A third problem has been that of discrepancies in evidence, aggravated at times by the fact that some of the scientific evidence in this field has been provided by so-called “Foundations” which have been all too closely linked to oestrogen manufacturing interests.

During the period 1996–1997, a group of US researchers advanced what they regarded as firm evidence that in this population oestrogens could substantially reduce the risk of contracting coronary disorders [1, 2], and their work tended to persuade others to adopt this view in their daily work [3]. In 1998 the pendulum tended to swing away from this belief, particularly with the publication of the first findings from a study of secondary oestrogen prophylaxis in women with already established coronary disease; these indicated that oestrogens had no effect on the occurrence of myocardial infarct or on cardiovascular (or total) mortality [4]. Some new observational studies pointed to the ability of oestrogens to reduce myocardial infarct [5] yet others did not. The much-publicized Nurses’ Health Study found a reduction by some 50% in the risk of infarct [6], though there was no reduction in total mortality. Many were impressed by a meta-analysis published by Barrett-Connor and others in the US in 1998 which concluded that with use of oestrogens the relative risk of suffering cardiac infarct was only 0.7 [7]. A suggestion made at one time that the risk of cerebrovascular accidents might be reduced by giving oestrogens has never been confirmed.

Any physician confused by these data, as well he might be, should bear in mind that in middle-aged women smoking is the most prominent risk factor for myocardial infarct, while raised serum cholesterol and high blood pressure are also important. On the other hand, the effect of the menopause, viewed in isolation, on coronary risk is not at all clear. This and other possible risk factors tend to get mixed up because they often co-exist. In the well-known Framingham study of 1985, for example, many of the women using hormones proved to have enjoyed a more favorable serum lipid spectrum before they even began hormonal treatment [8]. Similarly, it has been found that women using oestrogens tend to belong to the upper social groups in whom one encounters less obesity, more physical activity and (whether or not for these reasons) a better risk profile than those likely to enter a control group of non-users.

The fear that oestrogens might raise the risk of endometrial cancer has been noted above. There is also some reason to believe that that use of these hormones increases the risk of mammary carcinoma, while broad overviews of the literature strongly suggest that in the doses used for replacement therapy the risk of thromboembolic incidents may be significantly increased, perhaps by some 60%; the Framingham

study already cited suggested a raised incidence of cardiovascular problems, especially when hormone use was associated with smoking.

In view of the unclear safety-efficacy equation, it is not surprising that, as of the turn of the century, internists and gynaecologists are divided within their own specialisms on the question of oestrogen use. The only *proven* indication for using oestrogens alone (and then only for a limited period) remains symptomatic acute hypo-oestrogenism such as can occur in some women following a natural menopause and in the great majority of women who have undergone oophorectomy. Similarly, the only fully defensible use for oestrogen-progestagen combinations at the time of the menopause is to control heavy and irregular bleeding per vaginam. It is arguable that in women in whom there is a familial tendency to osteoporosis, oestrogens can be helpful for reducing its occurrence, though only as a supplement to adequate mineral intake. Beyond this, and while awaiting further investigations, one must sympathize with those who maintain that as of 2000, healthy and physically active women in mid-life with a favourable blood lipid spectrum do not need oestrogens to keep them healthy.

References

- [1] F. Grodstein, M.J. Stampfer, J.A.E. Manson et al., Postmenopausal estrogen and progestin use and the risk of cardiovascular disease, *N. Engl. J. Med.* **335** (1996), 453–461.
- [2] F. Grodstein, M.J. Stampfer, G.A. Colditz et al., Postmenopausal hormone therapy and mortality, *N. Engl. J. Med.* **336** (1997), 1769–1775.
- [3] S.T. Nilsen, T. Fredriksen, O.-E. Iversen et al., Norske gynekologers holdninger til og praksis ved hormonsubstitusjonsbehandling i klimakteriet, *Tidsskr Nor Laegeforen* **118** (1998), 2940–2943.
- [4] S. Hulley, D. Grady, T. Bush et al., Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women, *JAMA* **280** (1998), 605–613.
- [5] E. Barrett-Connor and J. Grady, Hormone replacement therapy, heart disease and other considerations, *Annu. Rev. Publ. Health* **19** (1998), 55–72.
- [6] M.J. Stampfer, G.A. Colditz, W.C. Willett et al., Postmenopausal estrogen therapy and cardiovascular disease, *N. Engl. J. Med.* **325** (1991), 756–762.
- [7] E. Barrett-Connor and D. Grady, Hormone replacement therapy, heart disease and other considerations, *Annu. Rev. Publ. Health* **19** (1998), 58–72.
- [8] P.W.F. Wilson, J. Garrison and W.P. Castelli, Post-menopausal estrogen use, cigarette smoking and cardiovascular mortality in women over 50. The Framingham Study, *N. Engl. J. Med.* **313** (1985), 1038–1043.