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Editorial

Álvaro Nagib Atallah

Coronary heart disease and estrogen plus progestin treatment: the "burden" of the evidence

Health professionals' enthusiasm for the prescribing of estrogens together with progestin in postmenopausal women received a major setback recently. The publication of a randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women[1] has brought to light some new evidence in the subject that is contrary to the previous "consensus". Growing evidence from observational studies among women receiving estrogens had been indicating some benefits of estrogens in the prevention of coronary heart disease in postmenopausal women. But this large randomized double-blind placebo-controlled trial, which aimed to determine whether estrogen/progestin therapy decreased the risk of coronary heart disease events in women with established coronary disease, showed that estrogens together with progestin have negative effects.

The study was done on 2.763 women with coronary disease. The treated group received 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily. The follow-up averaged 4.1 years and the adherence was good. The primary outcomes were non-fatal myocardial infarction or coronary heart disease death. 172 women in the hormone group and 176 in the placebo group had these primary events. This lack of overall effect occurred in spite of an 11% less low density lipoprotein cholesterol (LDL-c) level and a 10% greater high density lipoprotein cholesterol (HDL-c) level in the hormone group than in the placebo group ($P< 0.001$). Furthermore, there was a significant trend of more coronary heart disease events in the first year in the hormone group and fewer in the 3rd and 4th year. There were 34 thromboembolic events in the hormone group and 12 events in the placebo group (relative risk 2.89; 95% C.I. 1.50 to 5.58). Gallbladder disease was significantly more frequent in the hormone group than in placebo, with 84 versus 62 cases ($P= 0.05$).

The authors concluded that the treatment with oral conjugate equine estrogens plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease events in the studied patients and did not recommend the use this treatment for the purpose of secondary prevention of coronary heart disease.[1]

This trial is a well-performed study, was supported by the pharmaceutical industry and was published in spite of the negative results.

The situation described is yet another example of the need to wait for good evidence

that a treatment causes more good than harm before putting it into general practice. The initial enthusiasm for this treatment was based on observational studies, which are quoted as level of evidence IV or V for therapeutic decision making.[2]

Besides that a systematic review[3] of observational studies on 150,000 patients, showed a significant increase in breast cancer following hormonal replacement therapy was shown.

One criticism that can be made of the estrogen/progestin trial is that it only included patients with previous coronary heart disease, with a mean age of 66.7 years, leaving open the hypothesis that treatment for primary prevention in younger women could be beneficial. It is, however, not good decision-making practice to give treatment based on hypotheses and therefore we need to wait for a study aimed at answering such a question, because of its clinical implications. A larger study within the National Women Initiative, aiming to randomize 68,000 women, is underway and its publication is expected for the year 2007. The best existing evidence does not justify the use of estrogen together with progestin for the prevention of coronary heart disease in postmenopausal women.

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