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## Lipoprotein (a) concentrations in postmenopausal women taking norethisterone

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Hormone replacement therapy is effective in treating menopausal symptoms and preventing osteoporosis. Regimens usually consist of oestrogen or an oestrogen-progestogen mixture. Postmenopausal oestrogen substantially reduces the risk of death from cardiovascular disease, due in part to lipoprotein changes, particularly an increase in high density lipoprotein concentration. When oestrogen is contraindicated a progestogen only regimen may be used. The androgenic progestogen norethisterone, which can substantially improve climacteric symptoms and decrease bone loss, is commonly prescribed.<sup>1</sup> Norethisterone, however, adversely affects lipoprotein metabolism, causing a pronounced decrease in high density lipoprotein concentration.<sup>2</sup>

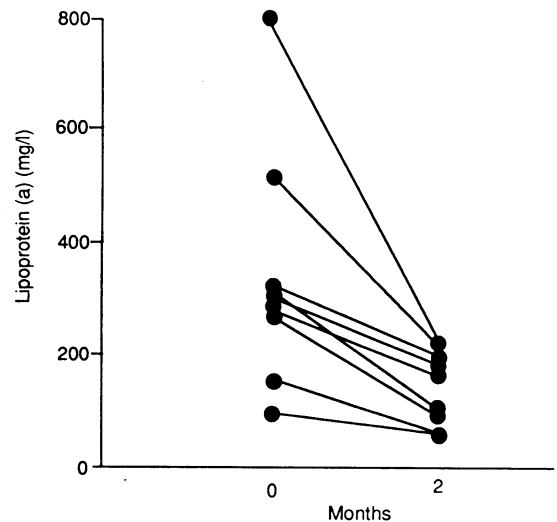
There has been an upsurge of interest in lipoprotein (a), high concentrations of which are associated with atherosclerosis. A growing body of evidence suggests that lipoprotein (a) is an important independent risk factor for cardiovascular disease with possibly greater predictive potential than the other lipoprotein risk markers. Most hypolipidaemic agents currently in use have little or no effect on lipoprotein (a).<sup>3</sup> Oestrogen reportedly has no effect on lipoprotein (a).<sup>4</sup> In contrast, the anabolic steroid stanozolol, used in postmenopausal osteoporosis, substantially decreases lipoprotein (a) concentrations.<sup>5</sup> Stanozolol has adverse effects, similar to those of norethisterone, on other lipoproteins. To our knowledge the effects of progestogens on lipoprotein (a) have not been studied. We have therefore carried out a small pilot study to see whether concentrations are affected by norethisterone.

### Patients, methods, and results

We studied nine women who had detectable lipoprotein (a) concentrations (>50 mg/l). Their average age was 50. Five had had bilateral oophorectomy at least two months before starting treatment. The other four had had a natural menopause, as judged by established amenorrhoea and postmenopausal gonadotrophin values. None had received any hormonal treatment before recruitment. All suffered from menopausal symptoms and were considered unsuitable for oestrogen treatment because of a history of thromboembolic disease. They were treated with norethisterone (Primolut N) 5 mg twice daily.

Fasting blood samples were obtained before treatment and after two months of treatment. Lipoprotein (a) was measured by an enzyme linked immunosorbent assay (ELISA; Immuno Ltd). Values at two months were compared with baseline by using Wilcoxon's matched pairs signed ranks test.

Pretreatment lipoprotein (a) concentrations ranged from 90 to 800 mg/l (median 300 mg/l). After two months the median concentration had fallen by 47% to 160 (range 60 to 220) mg/l ( $p < 0.01$ ). A decrease was recorded in every subject, the largest falls occurring in



Lipoprotein (a) concentrations in nine patients before and after two months of norethisterone

the two patients with the highest pretreatment values (figure).

### Comment

These findings may be important in relation to hormone replacement therapy. Although it has not as yet been shown that lowering lipoprotein (a) concentrations reduces the risk of cardiovascular disease, by analogy with the results of other risk factor studies it seems likely that such a change will be beneficial. Previous work on lipoproteins has indicated that norethisterone may be unsuitable for long term prophylaxis against osteoporosis.<sup>2</sup> Its effect on lipoprotein (a) concentrations, however, might, at least to some extent, offset its adverse effects on other lipoprotein risk factors.

Women who have not had hysterectomy who use postmenopausal oestrogens also receive a progestogen to protect them against endometrial cancer. Norethisterone is commonly used in combined preparations and there is concern that its effect on high density lipoproteins could partially negate the beneficial effects of oestrogen on the cardiovascular system. Our results suggest that the use of androgenic progestogens such as norethisterone may not be as deleterious as was previously feared. We suggest that in future hormone replacement studies lipoprotein (a) should be added to the lipoprotein risk markers currently monitored.

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