

This finding is statistically compatible with our results, as discussed in our report.

Grant and colleagues also mention "problems with the reference groups". We disagree. In our analyses of the effects of oral contraceptive use on mortality, we allowed for the effect of smoking and many other factors, using a well established and valid method. There was only a modest association between smoking and oral contraceptive use in our study anyway, with pill users being somewhat more likely to smoke than non-users. Our information on HRT use is incomplete, but we showed in our report that such use was slightly greater among oral contraceptive users than non-users. Both these weak associations—ie, between pill use and smoking, and pill use and HRT use—would tend to show mortality in oral contraceptive users in an unfavourable light rather than the reverse as Grant and colleagues seem to believe.

Grant and colleagues think we should compare the effects of smoking for given periods of time with the effects of oral contraceptive use for the same periods. We again disagree. Our comparisons are valid since oral contraceptive use usually extends over a moderate number of years, while smoking, sadly, often extends over a lifetime. We considered the effects of oral contraceptive use and of smoking in the way the two exposures arise in the community.

Finally, none of the women in our study who died from endometrial cancer or uterine sarcoma had breast cancer, so the comments about use of tamoxifen are irrelevant.

Our results offer reassurance about the effects of oral contraceptive use on mortality, both in the short term and in the long term. They refer, however, mainly to oral contraceptives used in the 1970s and 1980s, and further information is needed about more modern preparations.

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Genetic influence of hormone-replacement therapy on venous thromboembolism

Sir—Pierre-Yves Scarabin and colleagues' findings (Aug 9, p 428)¹ indicate that oral but not transdermal oestrogen-replacement therapy is associated with risk of venous thromboembolism (VTE) in postmenopausal women.

Among many risk factors for hypercoagulability—eg, malignant disease, immobility, smoking, obesity, diabetes, advanced age, heart failure—genetic variations in certain genes could explain the interaction between oestrogens and VTE risk. Mutations in coagulation factor II (prothrombin G20210A) and in coagulation factor V (Factor V Leiden) are, for example, associated with raised risk of venous thrombosis.²

Vandenbroucke and colleagues³ noted that premenopausal women who took oral contraceptives and who were carriers of the factor V Leiden mutation had a raised risk of deep vein thrombosis, and Psaty and co-workers' results⁴ indicate an association between hormone-replacement therapy (HRT), prothrombotic mutations, hypertension, and risk of incident non-fatal myocardial infarction in postmenopausal women. In view of these findings, we believe the interaction between transdermal HRT, genetic variants, and VTE should be investigated in postmenopausal women.

With respect to the effects of oral and transdermal HRT on haemostatic factors in postmenopausal women, Scarabin and co-workers⁵ have reported that oral HRT can result in coagulation activation and increased fibrinolytic potential, whereas transdermal HRT does not seem to substantially affect haemostasis. Thus, we propose that there might not be an interaction between transdermal HRT, genetic variants, and VTE in postmenopausal women, since there is no association between VTE risk and use of transdermal oestrogen.¹

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Edmonton's islet success has indeed been replicated elsewhere

Sir—As co-principal investigators of the Immune Tolerance Network multicentre clinical trial of the Edmonton Protocol, we wish to clarify the importance of the preliminary analysis.¹

A 90% insulin-free rate was noted in three centres with long-standing expertise in islet preparation and in the clinical use of this immunosuppressant protocol, not only at the Edmonton site where the protocol originated. The average rate of insulin independence among the remaining six clinical sites was 23%, including one site with an interim success rate of 67%.

Thus, the Edmonton Protocol has been replicated at other clinical sites and, in some cases, with a high degree of success.

Although these data are only preliminary, we view this result as a positive one, which confirms the great benefits to patients of islet transplantation and provides additional justification for the continued investigation of islet transplantation as a treatment for brittle forms of type 1 diabetes.

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