should be the chooser" when it comes to contraception, provided that she is fully informed. The committee's letter has added further complexity to the information that needs to be communicated.

Finally, in future how might distress among both prescribers and consumers be minimised when new research data affecting prescribing need to be conveyed? Difficult though it will always be, some system ought to be devised to ensure that the vast majority of doctors and pharmacists have received such information at least 24 hours ahead of the media. This can be achieved only with a rigidly enforceable embargo for the media. More importantly, such decisions should, except in extreme circumstances, be announced at the time of full publication of the data rather than weeks in advance. And might not future letters from the Committee on Safety of

Medicines incorporate input from actual prescribers of the treatment involved, including a user friendly A4 sheet that doctors could photocopy and give out to patients in their waiting rooms? Readers will doubtless wish to add to these suggestions.

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Third generation oral contraceptive pills

Is the scare over the increased risk of thrombosis justified?

Britain's Committee on Safety of Medicines has issued a recommendation that combined oral contraceptives containing the so called third generation progestogens, desogestrel and gestodene, should no longer be routinely prescribed. The committee came to this conclusion after examining the data from three unpublished studies, two of which have not been completed. These studies—an international study organised by the World Health Organisation; the European transnational study of oral contraceptives, which is funded by the pharmaceutical company Schering AG; and a study of data from the United Kingdom general practice research database (formerly known as VAMP)—were designed to examine whether the risk of vascular disease in women taking the newer oral contraceptive pills differed from that in women taking the slightly older pills containing predominantly the progestogen levonorgestrel. Analysis of data from the completed WHO study and interim analyses of the other studies' data suggest that the risk of venous thrombosis (mainly deep vein thrombosis of the leg) was approximately doubled in women taking the newer pills.

Inevitably there has been much questioning about whether this decision was justified. It is a basic tenet of epidemiology that a statistical association that arises from an observational study is not proof of causation. Chance, confounding, and bias are other possible (and not mutually exclusive) explanations. Of these, chance is the easiest to address: statistical tests give P values and confidence intervals that allow us to estimate the strength of the associations. The relevant associations in the three studies are mostly (but not entirely) significant in the sense that the P values are less than 0.05. The lower limits of the 95% confidence intervals, however, are generally in the region of 1.0-1.5 and are sometimes less than unity. So the point estimates do not indicate a strong association, and the lower limits of the confidence intervals are consistent with the true associations being minimal or non-existent.

Confounding means that the apparent association is due wholly or partly to another factor or factors. A confounder is a factor that is associated with both the possible risk condition (in this case, the use of oral contraceptives) and the outcome (venous thrombosis). Analyses of data from the WHO and transnational studies have included adjustments for the possible confounding effects of age, smoking, alcohol consumption, study centre, body mass index, and duration of use of oral contraceptives. Analyses of the transnational study data

have been carried out with hospital and community controls both separately and combined. Further analyses are planned because a number of epidemiological, medical, and statistical experts have advised the study team that residual confounding may still be present.

Bias is a more difficult issue. Of particular concern is the possible bias resulting from newer brands of oral contraceptive being prescribed to new users and to patients who are considered to be at higher risk, because doctors may have perceived the newer pills to be safer. In other words, do the effects of older and newer pills differ or is this finding due to the fact that the pills are prescribed to different groups of women?

The most disturbing issue, however, is the decision to base the warning solely on the likelihood of venous thrombosis. The rationale for the marketing of desogestrel and gestodene was their reduced effect, compared with that of older progestogens, on lipid and carbohydrate metabolism. The expectation was that they would be less likely to increase the risk of arterial disease—in particular myocardial infarction and stroke. Although these conditions are rare in young women, they are more likely than venous thrombosis to be fatal. For example, among the 11 million women aged 15-44 in England and Wales there were 18 deaths from venous thromboembolic disease in 1989 compared with 260 from myocardial infarction and stroke. All three studies had the potential to elucidate this important issue, and there must now be serious doubt that they can be continued long enough to produce valid conclusions. This is particularly important since preliminary data suggest that a protective effect against major cardiovascular events may already be apparent.

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