1 World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575-82.
2 Guillebaud J. Scare over oral contraceptives. *BMJ* 1995;311: 1638-9. (16 December.)
3 Faculty of Family Planning and Reproductive Health Care and Family Planning Association. *Response for doctors to the Committee on Safety of Medicines' letter of 18th October 1995.* London: FFPRHC, 1995.
4 Committee on Safety of Medicines. *Combined oral contraceptives and thromboembolism.* London: CSM, 1995.

Postmarketing surveillance does not catch all adverse events

EDITOR,—H B M Reijnen and W J Atsma, of Organon Pharmaceuticals, use data from the company's product surveillance database to show that the risk of venous thromboembolism with the pills Marvelon and Mercilon, both of which contain desogestrel, is highest in the first few months of use and falls dramatically thereafter.[1] The World Health Organisation's recent multicentre case-control study refutes this suggestion: the duration of current use of oral contraceptives did not alter the risk.[2]

What is worrying about the authors' letter is the fact that the product surveillance database contains data on only 434 adverse drug events, fewer than 100 of which are venous thromboemboli. With over 36 million woman years of exposure to these two pills, we can conservatively estimate that the total number of venous thromboemboli is over 5000. Thus the manufacturer's database has information on less than 2% of all such cases. The impressive graph accompanying the letter is simply a reflection of poor reporting getting progressively worse.

The database is highly selective, and its use in this debate is misleading. It also calls into question the methods of postmarketing surveillance.

This whole episode should make us reflect on the quality of evidence that we expect in our practice and how we came to adopt the newer progestogens. Was it reasonable to base a wholesale change in our prescribing practices on surrogate markers of arterial disease? Had we been a little more critical we might also now have reliable information on the benefits or otherwise of these pills with regard to such important side effects as weight gain, breakthrough bleeding, acne, and headache. Ethics committees may now refuse randomised controlled trials of these pills.

PAUL O'BRIEN
Session clinical medical officer

Raymede Clinic,
London W10 5SH

1 Reijnen HBM, Atsma WJ. Scare over oral contraceptives. *BMJ* 1995;311:1639. (16 December.)
2 World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575-82.

Study's results do not apply to norgestimate

EDITOR,—The issue of the *BMJ* published on 13 January contains two papers, an editorial, and two other items in which "third generation" oral contraceptives are discussed. At times third generation oral contraceptives are referred to as those containing gestodene, desogestrel, or norgestimate; at other times they are referred to as those containing gestodene or desogestrel. This may confuse readers.

In their paper on the risk of venous thromboembolic disorders associated with third generation oral contraceptives Walter O Spitzer and colleagues clearly state that for the purpose of their analysis "third generation oral contraceptives were defined as products containing low doses of ethinylestradiol (usually 30 μg or 20 μg) and either gestodene or desogestrel."[1] In the same paragraph the paper makes clear that "preparations containing norgestimate were included with the second generation products, to retain consistency with the World Health Organisation analysis." Inexplicably, however, in the "key messages" box in the paper one of the key messages refers to norgestimate as a third generation oral contraceptive and another states that third generation oral contraceptives are associated with an increased risk of thromboembolism.

Norgestimate was not associated with an increased risk of thromboembolism in this paper, and I am certain that the authors did not wish to imply otherwise. To prevent confusion among both doctors and women, care should be taken to avoid use of the broad term "third generation" in discussions of the recent publications on oral contraceptives and the risk of venous thromboembolism; rather, the names of the specific progestogens affected should be given.

R J DONNELLY
Medical director

Janssen-Cilag,
PO Box 79,
High Wycombe HP14 4HJ

1 Spitzer WO, Lewis MA, Heinemann, LAJ, Thorogood M, MacRae KD on behalf of Transnational Research Group on Oral Contraceptives and the Health of Young Women. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996;312:83-8. (13 January.)

Full description of controls is needed in study

EDITOR,—It is not uncommon to select controls from two sources because of concerns about the suitability of any one source. Superficial analysis of the data presented by Michael A Lewis and colleagues shows that hospital controls who use oral contraceptives are roughly three times less likely than community controls to use third generation pills (table 1).[1] Naively, one might conclude that third generation pills are a general tonic, particularly in comparison with second generation pills: women who use them are three times less likely to end up in hospital than those who do not use them (odds ratio 2·86 (exact 95% confidence interval 1·03 to 8·1)).

Table 1—*Use of oral contraceptives by hospital and community controls*

	No current use	Third generation pills	Second generation pills
Cases (hospital controls)	173	11	26
Community controls	246	23	19

χ^2 Test for independence: χ^2=5·97, 2 df, P=0·050.

Such a result should not, of course, be taken at face value but should lead us to question carefully the selection of controls in this study. Surprisingly, no details of why the hospital controls were admitted to hospital are given, either in the authors' two reports[1,2] or in the supplementary material posted on the Internet. The authors adjust their analyses for several variables, including age, body mass index, and smoking, but this seems only to increase the relative difference in the type of oral contraceptive used between the two groups (ratio of adjusted odds ratios 3·64).

By contrast, the authors of the World Health Organisation's paper on deep vein thromboembolism discuss their reasons for enrolling two types of controls and comment on the differences between these two groups in their study.[3] Essentially, they found that a much higher proportion of hospital controls than controls based in general practice used oral contraceptives but that the ratio of use of third to second generation pills was about the same in both groups. One might guess that hospital controls would better match for differences in use of hospital services whereas general practice controls would better match for variations in prescribing practice.

If controls are well chosen and the study is designed with adequate power there should be little difference in the distribution of the exposure of primary interest between the two groups. Particularly when this is not the case, a published report should contain a full description of each set of controls together with some discussion of the potential biases.

The problem of the appropriateness of a given set of controls serves to remind us of the pitfalls of observational studies and that they are a poor substitute for randomised controlled clinical trials.

PETER SASIENI
Research scientist

Department of Mathematics, Statistics, and Epidemiology,
Imperial Cancer Research Fund,
PO Box 123,
London WC2A 3PX

1 Lewis MA, Spitzer WO, Heinemann LAJ, MacRae KD, Bruppacher R, Thorogood M on behalf of Transnational Research Group on Oral Contraceptives and the Health of Young Women. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. *BMJ* 1996;312:88-90. (13 January.)
2 Spitzer WO, Lewis MA, Heinemann LAJ, Thorogood M, MacRae KD on behalf of Transnational Research Group on Oral Contraceptives and the Health of Young Women. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996;312:83-8. (13 January.)
3 World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestogens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995;346:1582-8.

Authors' reply

EDITOR,—Peter Sasieni is correct in asserting that a randomised controlled clinical trial is stronger than an observational case-control study. When concerns exist about the safety of drugs that are already being marketed, however, randomised controlled trials are seldom feasible. Most issues of drug safety concern very small risks. In the case of venous thromboembolic disease, a rough estimate of the baseline population risk is one event in 10 000 woman years. Given this annual incidence of 0·0001 in unexposed women, with a two tailed α of 0·05, a β of 0·2, and a ratio of controls to exposed subjects of 1:1, each group would need to contain about 300 000 women to detect a relative risk of 2 and about 60 000 women to detect a relative risk of 4.[1] These sample sizes clearly render a randomised controlled trial impractical. The background incidence of acute myocardial infarction among this population is even smaller than that of deep vein thrombosis, so a case-control approach is mandatory. Even a cohort study is almost impossible except with large computerised databases.[2]

A major difficulty with case-control studies is, as Sasieni states, the appropriate choice of controls. This is why we planned two sets of controls in the transnational study, to reflect the use of oral contraceptives in the general population and in hospital controls. Contrary to Sasieni's belief, the details of the controls and the rationale for choosing them were published before we started our fieldwork.[3] The protocol stated our intention of collecting 200 cases of acute myocardial infarction, but the study was thwarted by publicity bias resulting from the actions of the Committee on Safety of Medicines. Largely because of public demand, we published the results at that point; they were based on the 153 cases of acute myocardial infarction that had accrued. Because we were aware of the discrepancy between the hospital