south Wales, and our list size is 5600. All consultations in this context were initiated by patients.

We routinely code clinical information during consultations on our computer database; this facilitates audit of clinical practice. When a patient is advised about contraception a Read code (6777: contraception counselling) is recorded. Over the 10 weeks before the "pill scare" on 19 October the code for contraception counselling was recorded 18 times (average 1.8 times a week). Over the three weeks after the announcement the code was recorded (week by week) 30, 28, and 27 times (average 28.3).

If it is assumed that these figures are reflected throughout England and Wales the effect on general practitioners' workload nationally can be estimated and perhaps costed.

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1 Health Commissioning Division. *Pharmaceutical hazard warning No 580*. Cardiff: Welsh Office, 1995.

Main public health issue is failure to use contraception

EDITOR,—The letter from the Committee on Safety of Medicines to all doctors about the increased risk of thromboembolism in women taking oral contraceptives containing desogestrel and gestodene,¹ and the manner in which it was released to the press, has caused predictable public panic. Surely the data should have been presented in the context of the wider issue of the provision of effective contraception. As has been pointed out, protective effects against other diseases must also be balanced, but most importantly the data must be viewed alongside figures for termination of pregnancy (which is only one of the possible outcomes of unwanted pregnancy caused by ineffective contraception).^{2,3}

In Scotland in 1993, 1% of women aged 15–44 had a termination of pregnancy, and the cumulative percentage of 25–44 year olds who had had a termination of pregnancy was 15%.⁴ The physical and psychological sequelae are well documented. Such figures suggest a much larger public health concern—namely, underuse of contraception.

I recently studied the provision of contraception at Springburn Health Centre, a general practice in inner city Glasgow run by Dr M R McLaughlin and partners. An initial audit showed that the practice was providing contraceptive services to 165 out of 770 women aged 16–45. The remaining 505 women were surveyed opportunistically over the next nine months (244 (48%) were seen). The women were asked whether they attended elsewhere for family planning (for example, a family planning clinic), whether they did not require contraception (for example, because they were sexually inactive or had had a hysterectomy), or whether they had an unmet need for contraceptive services. Only 15 attended elsewhere, 174 had no requirement for contraception, and 55 required contraception. Analysis by age group showed that 8 of the 24 women aged 16–20, 20 of the 41 aged 21–25, 20 of the 105 aged 26–35, and 7 of the 74 aged 36–45 required contraception.

Such figures support the view that the main public health issue is failure to use contraception at all, let alone effectively. While I agree that research on the safety of methods of contraception is essential, the Committee on Safety of Medicines must surely have realised that its letter would be sensationalised and should not be presented to the press in isolation.

Evidence already exists that fear about the safety of contraception prevents the public from seeking advice.⁵ Many doctors will share my fear that an

erroneous "take home message"—that the pill is dangerous—will be yet another barrier to overcome for those trying to promote and provide safe, effective advice on family planning.

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- 1 Committee on Safety of Medicines. *Combined oral contraceptives and thromboembolism*. London: CSM, 1995.
- 2 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111–2. (28 October.)
- 3 MacRae K, Clifford K. Third generation oral contraceptive pills. *BMJ* 1995;311:1112. (28 October.)
- 4 Office of Population Censuses and Surveys. *Abortion statistics 1993*. London: HMSO, 1994. (Series AB No 20.)
- 5 Zabin LS, Stark HA, Emerson MR. Reasons for delay in contraceptive clinic utilization. Adolescent clinic and nonclinic populations compared. *J Adolesc Health* 1991;12:225–32.

New group will review evidence for effective care in family planning

EDITOR,—One of the problems in the provision of family planning is the dearth of useful, clinical randomised controlled trials on which to base our practice. For some rare events such as thrombosis, heart attacks, and stroke, randomised controlled trials are clearly not feasible and we rely on the epidemiological data from well conducted studies. Some factors, however, are readily amenable to randomisation. John Guillebaud suggests that it would be appropriate for a client to start taking a pill containing desogestrel or gestodene if the predictable incidence of breakthrough bleeding, acne, headache, and weight gain with alternative pills is higher.¹ It is extraordinary that, although three million women in Britain are using the pill for contraception, we have little evidence to support this advice.

I have performed a Medline search, from 1976 to the present, for randomised controlled trials comparing these minor side effects associated with second generation pills with those associated with the newer combined pills containing desogestrel or gestodene and found only one trial. In a randomised trial of 456 women Loudon *et al* found a reduced incidence of breakthrough bleeding with a pill containing gestodene compared with one containing levonorgestrel but no difference in weight gain.² There is no evidence on headache and acne.

The Cochrane Collaboration, which prepares, maintains, and disseminates systematic reviews of the effects of health care, will be organising an exploratory meeting early next year with a view to establishing a Fertility Control Cochrane Review Group. The aim of the group will be to review the evidence for effective care in family planning. This will involve an extensive search for published and unpublished trials and the preparation of systematic reviews for wide distribution. Anyone interested in this project can contact me for further details.

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- 1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111–2. (28 October.)
- 2 Loudon NB, Kirkman RJ, Dewsbury JA. A double-blind comparison of the efficacy and acceptability of Femodene and Microgynon-30. *Eur J Obstet Gynecol Reprod Biol* 1990;34:257–66.

Doctors should take warning seriously

EDITOR,—I wish to challenge John Guillebaud's editorial¹ on the recent warning by the Committee on Safety of Medicines about combined oral contraceptives containing gestodene and desogestrel.² Some family planning doctors will not agree with his views on a continued role for preparations that seem to double the risk of venous thrombo-

embolism for current users compared with users of low dose monophasic oral contraceptives containing levonorgestrel and norethisterone. There is no evidence from epidemiological studies that preparations containing levonorgestrel and norethisterone carry a comparatively greater risk of excess deaths from myocardial infarction or stroke. It is virtually impossible to show an increased risk of myocardial infarction in current or past users of any combined oral contraceptive formulation if they have avoided higher dose preparations, provided that they do not smoke.³ It hardly seems necessary, therefore, to make premature claims for formulations that may protect women from a barely identifiable risk.

Claims that the combined oral contraceptives containing gestodene and desogestrel may protect women from myocardial infarction are apparently based on the theory that a decreased high density lipoprotein cholesterol concentration is an appropriate single marker for the risk of myocardial infarction in premenopausal women. This is dubious because a reduction in high density lipoprotein cholesterol concentration in premenopausal women without a concomitant increase in total cholesterol or triglyceride concentration, or both, is unlikely to increase the risk of myocardial infarction.⁴ Moreover, metabolic studies tend to be conducted on small numbers of women for relatively short periods and to report mean changes that are still within normal limits. There is a considerable margin of error and interlaboratory disagreement. One reported study on which much reliance was placed is now known to have been fraudulent.⁵ There is probably considerable reporting bias, and the few published randomised comparative studies of older and newer pills containing progestogen offer conflicting results.

Doctors will be well advised to take seriously the letter from the Committee on Safety of Medicines about the risk of venous thromboembolism and to reserve their judgment on other possible cardiovascular risks of combined oral contraceptives until more definitive epidemiological evidence is published.

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- 1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111–2. (28 October.)
- 2 Committee on Safety of Medicines. *Combined oral contraceptives and thromboembolism*. London: CSM, 1995.
- 3 Thorogood M, Mann J, Murphy M, Vessey M. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study. *Br J Obstet Gynaecol* 1991;98:1245–53.
- 4 Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373–81.
- 5 Briggs MH. Recent biological studies in relation to low dose hormonal contraceptives. *British Journal of Family Planning* 1979;5:25–8.

If a woman has not had a thrombotic event in years of use she is unlikely to have one now

EDITOR,—My editorial commenting on the letter from the Committee on Safety of Medicines and the three studies that gave rise to it had to be cut because of lack of space.¹ In the original version I argued that, in these trials, the proportion of women who had been exposed in the past to ethinylloestradiol (in any combination) might be higher among current users of the third generation pills containing desogestrel and gestodene; ethinylloestradiol is still recognised as the prime prothrombotic constituent of contraceptive pills. This difference would effectively mean that a smaller proportion of women taking the longer established pills had hereditary disorders of coagulation (since such women would have stopped

using the pill early because they had had a thromboembolic event). The users of products containing levonorgestrel and norethisterone might then comprise, in effect, a population of survivors who are less at risk of the condition under study. I understand that further analyses are in progress to test this hypothesis in various ways.

The same model, however, has important implications for prescribers now. A first time user could have an undiagnosed congenital or acquired abnormality of coagulation or fibrinolysis,² which would put her into what is believed to be the main minority group, in whom the small incremental changes caused by the pill are able to reach the threshold for a thrombosis. On the other hand, the established user of ethinyloestradiol (even if this is combined with a third generation progestogen) has, by her continuation with the drug for years without problems, shown her relative insusceptibility to venous thrombosis.

This argument means, firstly, that, should women taking third generation pills fail to respond to the current publicity, there is no pressing urgency to recall them for a discussion of the possibility of changing their brand. If it is logistically possible, however, it would be preferable medicolegally to contact those who are known to be predisposed to thrombosis (through obesity, for example). Secondly, might not the Committee on Safety of Medicines have used this same argument as the basis for a much less pressurised warning, recommending discussion of a possible change of prescription at women's next routine visit concerning the pill?

A useful additional point to make while counselling a woman who has taken the pill for several years is that, though her risk is never zero, as she has not had a venous thrombosis during these years she is particularly unlikely to have one. "The informed user should be the chooser."

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1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111-2. (28 October.)

2 Machin SJ, Mackie JJ, Guillebaud J. Factor V Leiden mutation, venous thromboembolism and combined oral contraceptive usage. *British Journal of Family Planning* 1995;21:11-2.

Committee's action has compromised continuing studies

EDITOR,—Douglas Carnall's report of the controversy over whether the third generation contraceptive pills are associated with an increased risk of thrombosis contains an error that illustrates how bias may arise in a case-control study such as that led by Professor Walter Spitzer.¹ Carnall states that the study "matches 980 users of the combined pill who have a cardiovascular event with 2200 controls." In fact, the study matched 870 women who developed the disease of interest—that is, cardiovascular events—with 2900 matched controls. A large percentage of these women were not taking or had never taken a combined pill.

Bias could have arisen in the study if recruiting physicians, with the best of intentions, actively recruited women using the pill who developed the disease of interest. We believe that this may have happened in some instances, which would artificially inflate the risk. We continue to check the data for bias. This possibility also illustrates the possible danger inherent in hasty action before careful review of the data. The action of the Committee on Safety of Medicines has clearly compromised important, continuing studies such as the one with which we are involved.

We urge that further action should not be taken until the peer reviewed data are available for scrutiny and regulatory bodies can agree on a single course of action for a problem that is clearly

worldwide. The ultimate decision must involve a balancing of the risks of thrombotic events with possible protection against myocardial infarction.

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1 Carnall D. Controversy rages over new contraceptive data. *BMJ* 1995;311:1117-8. (28 October.)

Risk is highest during first months of use

EDITOR,—The well known association between use of oral contraceptives and venous thromboembolism received renewed interest when the results of three unpublished epidemiological studies suggested that the newer oral contraceptives containing third generation progestogens are associated with an increased risk of venous thromboembolism compared with the older oral contraceptives.^{1,2} Part of the explanation for this could be the shorter average duration of use of the newer oral contraceptives: if the risk of venous thromboembolism was highest during the first months of use it would be lower among women who had taken their oral contraceptive for longer than this without complications. To test this hypothesis we analysed spontaneous reports of adverse drug events received by NV Organon.

We looked at all spontaneous reports of venous thromboembolic events associated with the use of Marvelon (150 µg desogestrel and 30 µg ethinyloestradiol) and Mercilon (150 µg desogestrel and 20 µg ethinyloestradiol) entered into the product surveillance database up to 1 July 1995. We calculated (or estimated) the interval between the time when the contraceptive was started and the time when the event occurred. The figure shows the distribution of duration of use relating to the venous thromboembolic events (both drugs combined). Nearly half of the events occurred within the first six months of use.

The figure suggests a strong effect of duration of use on the risk of venous thromboembolism. Several limitations should be borne in mind. Firstly, the longer women have used oral contraceptives the less able they are to recall the date of

Reports of venous thromboembolic events as percentage of all adverse drug events associated with Marvelon and Mercilon (n=434) by duration of use (estimated total exposure is over 36 million woman years)

the start of treatment accurately. This, however, will lead to an underestimation of the effect as it will result in non-differential misclassification over the strata of duration of use. Secondly, the pattern of our findings should be contrasted with the overall distribution of duration of use of oral contraceptives in the general population. As the mean duration of use in the general practice research database study exceeded 16 months (H Jick *et al*, unpublished findings) high rates of early discontinuation cannot explain the sharp decrease in the rate of reporting over the first months of use shown in the figure. Thirdly, use of spontaneous reports could introduce bias since the tendency to report an event decreases with increasing duration of use. There is no reason to suspect, however, that doctors would be more likely to report a thrombotic event associated with short term than with long term use.

Our findings are consistent with an effect of duration of use: the risk of venous thromboembolism is higher during the first months of use. A consequence of this could be that when short term use of a certain type of oral contraceptive is overrepresented in a dataset the risk of venous thromboembolism associated with that type of contraceptive will be overestimated if appropriate adjustment is not made.

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1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111-2. (28 October.)

2 MacRae K, Kay C. Third generation oral contraceptive pills. *BMJ* 1995;311:1112. (28 October.)

Studies implicate only gestodene and desogestrel

EDITOR,—The Committee on Safety of Medicines' advice to the profession on combined oral contraceptives led to two editorials^{1,2} and three other items.^{3,4} All the authors, apart from Naomi Craft,⁵ incorrectly reported the committee's warning as extending to all "third generation" or "newer" combined oral contraceptives, whereas these two terms do not appear in the committee's letter. The committee's warning related only to desogestrel and gestodene. In addition, the committee recommended that "No change in prescribing practice is required for any other combined oral contraceptive."

Janssen-Cilag markets Cilest, a combined oral contraceptive that contains the third generation progestogen norgestimate. I hope that my letter corrects any confusion that readers may have about Cilest's position.

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1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111-2. (28 October.)

2 MacRae K, Kay C. Third generation oral contraceptive pills. *BMJ* 1995;311:1112. (28 October.)

3 Carnall D. Controversy rages over new contraceptive data. *BMJ* 1995;311:1117-8. (28 October.)

4 Spitzer WO. Data from transnational study of oral contraceptives have been misused. *BMJ* 1995;311:1162. (28 October.)

5 Craft N. Clots of trouble. *BMJ* 1995;311:1172-3. (28 October.)

Committee's action will undermine further research and development

EDITOR,—We deplore the failure of the Committee on Safety of Medicines and its chairman, Professor Michael Rawlins, to understand the issues raised by their hasty and ill considered advice to doctors not to prescribe oral contraceptives containing the