Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis

Hershel Jick, James A Kaye, Catherine Vasilakis-Scaramozza, Susan S Jick

Editorial by Skegg

Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA 02421, USA
Hershel Jick *associate professor of medicine*
James A Kaye *epidemiologist*
Catherine Vasilakis-Scaramozza *epidemiologist*
Susan S Jick *associate professor of epidemiology and biostatistics*
Correspondence to: H Jick hjick@bu.edu

BMJ 2000;321:1190–5

Abstract

Objective To compare the risk of idiopathic venous thromboembolism among women taking third generation oral contraceptives (with gestodene or desogestrel) with that among women taking oral contraceptives with levonorgestrel.
Design Cohort and case-control analyses derived from the General Practice Research Database.
Setting UK general practices, January 1993 to December 1999.
Participants Women aged 15-39 taking third generation oral contraceptives or oral contraceptives with levonorgestrel.
Main outcome measures Relative incidence (cohort study) and odds ratios (case-control study) as measures of the relative risk of venous thromboembolism.
Results The adjusted estimates of relative risk for venous thromboembolism associated with third generation oral contraceptives compared with oral contraceptives with levonorgestrel was 1.9 (95% confidence interval 1.3 to 2.8) in the cohort analysis and 2.3 (1.3 to 3.9) in the case-control study. The estimates for the two types of oral contraceptives were similar before and after the warning issued by the Committee on Safety of Medicines in October 1995. A shift away from the use of third generation oral contraceptives after the scare was more pronounced among younger women (who have a lower risk of venous thromboembolism) than among older women. Fewer cases of venous thromboembolism occurred in 1996 and later than would have been expected if the use of oral contraceptives had remained unchanged.
Conclusions These findings are consistent with previously reported studies, which found that compared with oral contraceptives with levonorgestrel, third generation oral contraceptives are associated with around twice the risk of venous thromboembolism.

Introduction

In December 1995 three independent studies reported around a twofold increased risk of venous thromboembolism in women who used the so called third generation combined oral contraceptives (those containing the progestogens desogestrel or gestodene together with 30 µg or less of oestrogen) compared with a second generation oral contraceptive with levonorgestrel and similarly low dose oestrogen.[1–3] One of the studies was derived from a large longitudinal computerised medical database known as the General Practice Research Database.[2] Several studies on this subject have since been published, some of which have reported results similar to the initial three studies and others no increased risk from third generation oral contraceptives.[4–9] This controversial issue has been discussed in two recent reviews.[10 11]

The background to this issue is related to a warning issued by the Committee on Safety of Medicines in October 1995 to all doctors and pharmacists. It stated that third generation oral contraceptives had been associated with around twice the risk of venous thromboembolism compared with levonorgestrel, a second generation oral contraceptive. It advised against using third generation oral contraceptives in women with risk factors for venous thromboembolism, such as obesity or prior venous thromboembolism. Subsequent to the scare the use of third generation oral contraceptives decreased dramatically in the United Kingdom, and the use of many other oral contraceptives including those with levonorgestrel consequently increased.[12]

The most recently published paper by Farmer et al based on the General Practice Research Database compared the risks of "idiopathic" venous thromboembolism in all current users of oral contraceptives with low dose oestrogen before and after the scare to evaluate the effect of the reduced use of third generation oral contraceptives on the incidence of venous thromboembolism.[13] They proposed that if third generation oral contraceptives doubled the risk of venous thromboembolism compared with oral contraceptives with levonorgestrel and if the use of third generation oral contraceptives was noticeably reduced after the warning, the overall incidence of venous thromboembolism should also have been reduced after October 1995. They interpreted their results as showing no decrease in the overall incidence of venous thromboembolism for all oral contraceptives after the

scare, and they concluded that this provided additional proof that the original findings by others were spurious. As the conclusions of Farmer et al were widely reported in the public press, we decided to conduct a study also based on the General Practice Research Database. We aimed to further evaluate the risk of venous thromboembolism, comparing third generation oral contraceptives with oral contraceptives with levonorgestrel, and to estimate and compare the overall incidence and relative risks of venous thromboembolism in users of these products before and after the scare.

Participants and methods

The General Practice Research Database has been fully described.[14] It provides virtually complete information on personal characteristics, drugs prescribed, clinical diagnoses, and numerous additional notations related to the diagnoses for over 3 million people, with follow up for as long as 12 years. Participating doctors were initially trained for one year to record the relevant information in a standard manner. Certain crude validation tests were applied to determine if the recorded data were satisfactory. Our research group began receiving the data in 1988. We updated the information at three month intervals, and we applied additional validation procedures to determine whether the practices were continuing to provide information of satisfactory quality. Over the past 12 years we have removed over half of the original practices because of inadequate data quality.[14 15] A critical aspect of the validation evaluation is the review of both the information recorded on computer and the required information on clinical records for tens of thousands of patients who have participated in the many studies we have conducted.

There are over 40 000 codes for "diagnoses and procedures" in the coding dictionary used by the research database and over 100 000 codes for drugs prescribed. Occasionally, however, illnesses or drugs (such as warfarin) are not coded in the standard way. For example, illnesses requiring surgery are often noted only by the operative procedure—for example, appendicitis is usually recorded only as appendectomy (code K444). These characteristics of the database necessitate careful review of patients' computerised records to ensure identification of all relevant illnesses, procedures, and treatments (potential proximate causes of idiopathic venous thromboembolism), because automated computer searches invariably fail to consider important clinical information.

Admissions to hospital and referrals are indicated in a special field. For new medical problems we estimate that this is about 90% complete since 1993 in the practices currently used for study.[2 6 7] In addition, there is a code for hospital admission (L34496HH) that is noted in the diagnostic field when there is no notation in the field normally used to indicate type of visit.

Study design

The basic design of our study was similar to that of many previous studies by our research group on drug related venous thromboembolism,[2 6 7] with the exception that we had insufficient time to obtain medical case histories for referrals and records from admission to hospital, as we had done in all of our previous studies. Thus the women in our study were identified as patients with idiopathic venous thromboembolism solely on the basis of a careful individual review of the computerised medical information for each patient with a first diagnosis of venous thromboembolism. These reviews were done by three investigators with experience in the study of drug related venous thromboembolism who were blinded to the type of oral contraceptive used. All patients included in the reviews received anticoagulants.

As in our previous study, this investigation was restricted to current users of either third generation oral contraceptives or oral contraceptives with levonorgestrel. We excluded women with less than one year's information recorded on computer, those with a recent diagnosis of injury to the lower limb, those who were pregnant or who had delivered up to three months previously, those who had undergone surgery in the previous two months or had recent arthroscopic procedures of the knee, those with cancer or other relevant benign tumours (for example, of the knee or pelvis), and those with recent severe trauma. Cases with these exclusions for apparent proximate causes of venous thromboembolism were identified by review of individual computer records, with blinding for type of oral contraceptive.

The remaining women, who were included as cases of venous thromboembolism, had no apparent proximate cause for venous thromboembolism present in the computer record, and all had had anticoagulants. A few of these women did not have prescriptions for warfarin coded as such but had other notations that established that they had received anticoagulants.

Cohort analysis

The two study periods were from January 1993 to October 1995 (period 1) and from January 1996 to December 1999 (period 2). To estimate person time at risk for each study drug we accumulated the time from the date of the first prescription for oral contraceptives in period 1 (after 1 January 1993) plus 28 days for each pill pack until the first of the following occurred: use of oral contraceptive was stopped; a different study oral contraceptive was prescribed; the woman died, was transferred out of the practice, or became a case; or the study period ended. Some practices stopped providing information before 1999 because of a change in their computer software, but person time contributed by those practices was valid and included in our analysis until such a change occurred.

Summary incidence ratios for the two periods were calculated, adjusting for age with both the Mantel-Haenszel method and indirect standardisation. The summary incidence ratio for third generation oral contraceptives versus oral contraceptives with levonorgestrel was calculated with the Mantel-Haenszel method to adjust for year of age.

Case-control analysis

We conducted a nested case-control analysis, with matching by year of age, practice, and date of diagnosis. We studied the periods separately and together to estimate the odds ratios for venous thromboembolism with third generation oral contraceptives compared with oral contraceptives with levonorgestrel. As in the cohort analysis, all cases and controls had to be current users of a study oral contraceptive. The exclusions for

Table 1 Number (percentage) of person years of use of oral contraceptives in study population according to age groups during study period 1 (January 1993 to October 1995) and study period 2 (January 1996 to December 1999)

Oral contraceptive	Age 15-19	Age 20-24	Age 25-29	Age 30-34	Age 35-39	Total
Study period 1						
Levonorgestrel	4 800 (17.9)	19 600 (28.9)	28 200 (42.2)	21 800 (46.8)	9 200 (44.5)	83 600
Third generation	22 200 (82.1)	48 200 (71.1)	38 600 (57.8)	24 700 (53.2)	11 500 (55.6)	145 200
Total	27 100	67 800	66 800	46 400	20 700	228 900
Study period 2						
Levonorgestrel	14 300 (88.6)	26 200 (78.9)	30 800 (79.5)	24 600 (83.7)	12 300 (82.0)	108 100
Third generation	1 800 (11.4)	7 000 (21.1)	8 000 (20.6)	4 800 (16.4)	2 700 (18.0)	24 300
Total	16 100	33 200	38 800	29 400	15 000	132 500

controls were the same as for cases. Although exclusions were common in the case group, they were rare (less than 2%) in the larger control series, indicating that the exclusion conditions were strongly associated with venous thromboembolism. Conditional logistic regression analyses were adjusted for body mass index and smoking history as well as duration of use of any oral contraceptive and whether or not participants had ever switched oral contraceptive preparations.

Results

Cohort analysis

The study population comprised 361 724 women who received 1 137 116 prescriptions for oral contraceptives with levonorgestrel and 979 052 women who received prescriptions for oral contraceptives with desogestrel or gestodene. These women contributed a total of about 361 300 person years of observation: 191 800 for oral contraceptives with levonorgestrel and 169 500 for third generation oral contraceptives. Table 1 lists the person times for users of the two types of oral contraceptives separately for the two periods, stratified by five year age group. Within every age group in period 2 the proportion of users of third generation oral contraceptives decreased substantially from that of period 1. The change was particularly striking among younger women—for example, among women aged 15-19 years, the use of third generation oral contraceptives decreased from 82% to 11% of the person time contributed by all oral contraceptive users in the study population.

We identified 106 cases of idiopathic venous thromboembolism in the study population: 42 among users of oral contraceptives with levonorgestrel and 64 among users of third generation oral contraceptives. Period 1 contained 71 cases (16 of whom were in our previous report[2]) and period 2 contained 35 cases. Table 2 shows that during both periods the crude incidence of venous thromboembolism was higher for third generation oral contraceptives than it was for oral contraceptives with levonorgestrel. In this cohort analysis, the crude incidence ratio for venous thromboembolism in women using third generation oral contraceptives compared with oral contraceptives with levonorgestrel was 1.7 (95% confidence interval 1.1 to 2.6). After adjustment for age (by year) with the Mantel-Haenszel method, the incidence ratio during the two periods combined was 1.9 (1.3 to 2.8); adjustment for age (by year) with Poisson regression yielded the same result. Thus, the cohort analysis showed that third generation oral contraceptives are associated with around twice the risk of venous thromboembolism compared with oral contraceptives with levonorgestrel. This is, however, a relatively crude analysis because there is no control for practice, body mass index, smoking, or duration of oral contraceptive use, and the control of calendar time is limited to year of diagnosis.

The age adjusted (Mantel-Haenszel) incidence ratio for venous thromboembolism in period 2 compared with period 1 among users of third generation oral contraceptives and oral contraceptives with levonorgestrel was 1.0 (0.5 to 2.0) and 1.2 (0.7 to 2.2), respectively. These results are not adjusted for calendar time within periods. Indirect standardisation (applying the incidence from period 1 to the age specific person time distribution in period 2) yields similar results, further supporting the conclusion that the incidence of venous thromboembolism associated with levonorgestrel and with third generation oral contraceptives did not differ materially between the two periods when age was taken into account.

Matched case-control analysis

We matched up to six controls for each of the 106 cases of venous thromboembolism that occurred among current users of third generation oral contraceptives or oral contraceptives with levonorgestrel. Matching factors were year of birth, practice, and index date—that is, controls had to be current users of either type of oral contraceptive on the date that their corresponding case developed venous thromboembolism. Overall, 569 controls were identified. The mean ages of

Table 2 Incidence and rate ratios for idiopathic venous thromboembolism comparing third generation oral contraceptives with oral contraceptives with levonorgestrel during two study periods (separately).

Study period	Progestogen	Women with venous thromboembolism	Woman years at risk	Crude incidence per 100 000 person years (95% CI)	Adjusted incidence ratio (95% CI)†
1 (January 1993 to October 1995)	Levonorgestrel	17	83 600	20.3 (11.8 to 32.5)	1.0
	Desogestrel or gestodene	54	145 200	37.2 (27.9 to 48.5)	2.0 (1.2 to 3.4)
2 (January 1996 to December 1999)	Levonorgestrel	25	108 100	23.1 (15.0 to 34.1)	1.0
	Desogestrel or gestodene	10	24 300	41.1 (19.7 to 75.6)	1.7 (0.8 to 3.5)

†Mantel-Haenszel method adjusting for age by year.

cases and controls were 28.7 and 28.5 years, respectively. Body mass index was known for 94 cases (mean 26.5) and 514 controls (mean 23.3). Other characteristics of the cases and controls are listed in table 3.

The matched case-control analysis yielded an estimated odds ratio for venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel of 2.2 (1.1 to 4.3) for period 1, 2.8 (1.1 to 7.3) for period 2, and 2.3 (1.3 to 3.9) for both periods combined (table 4). Our case-control analysis indicates that the risk of venous thromboembolism is more than twice as high among users of third generation oral contraceptives than it is among users of oral contraceptives with levonorgestrel, and the difference is significant. The relative risks compared with oral contraceptives with levonorgestrel were similar for oral contraceptives with gestodene (odds ratio 1.9, 1.0 to 3.8), desogestrel with 20 µg oestrogen (2.0, 0.9 to 4.8), and desogestrel with 30 µg oestrogen (2.8, 1.5 to 5.3). Both high body mass index (greater than 25, odds ratio 6.4, 2.6 to 15.5) and moderately high body mass index (20-25, 2.4, 1.0 to 5.7) were associated with an increased risk of venous thromboembolism compared with women with low body mass index (<20). Smoking was also found to be associated with an increased risk of venous thromboembolism (2.0, 1.3 to 3.3 compared with non-smokers and ex-smokers).

Any combination of oral contraceptive use before the index date of less than six months' duration was independently associated with a significantly increased risk of venous thromboembolism (3.8, 1.8 to 8.0 compared with users for seven months or more), and this effect is observed for both types of oral contraceptive. Prior switching of oral contraceptive preparations did not independently predict any change in the risk of venous thromboembolism when duration of use was taken into account.

The mean body mass index for controls who used oral contraceptives with levonorgestrel compared with controls who used third generation oral contraceptives was 23.5 versus 23.1 in period 1 (P=0.34) and 23.7 versus 22.4 in period 2 (P=0.04). Thus there is some evidence that doctors decreased their prescribing of third generation oral contraceptives to more obese women after the warning. Similarly, during period 1 (when 28.8% of all controls were smokers) 71 of 235 controls who used third generation oral contraceptives (30%) smoked compared with 7 of 31 (23%) during period 2 (when 28.5% of all controls were smokers). Thus the evidence shows that doctors may also have taken smoking behaviour into account after the warning when deciding on which oral contraceptive to prescribe.

Table 3 Characteristics of cases and controls. Values are numbers (percentages)

Characteristic	Cases (n=106)	Controls (n=569)
Age		
15-19	10 (9.4)	54 (9.5)
20-24	18 (17.0)	96 (16.9)
25-29	29 (27.4)	163 (28.7)
30-34	30 (28.3)	157 (27.6)
35-39	19 (17.9)	99 (17.4)
Body mass index (kg/m^2)		
<20	7 (6.6)	91 (16.0)
20-25	41 (38.7)	292 (51.3)
>25	46 (43.4)	131 (23.0)
Unknown	12 (11.3)	55 (9.7)
Smoking status		
Smoker	41 (38.7)	158 (27.8)
Non-smoker	61 (57.6)	393 (69.1)
Unknown	4 (3.8)	18 (3.2)
Any use of oral contraceptives (months)*		
1-6	16 (15.1)	32 (5.6)
7-12	9 (8.5)	57 (10.0)
>12	81 (76.4)	480 (84.4)
Switchers†	30 (28.3)	165 (29.0)

*Before index date.
†Women who used more than one type of combination oral contraceptive before their index date.

Table 4 Distribution of exposure to oral contraceptives in cases and controls and adjusted odds ratios of idiopathic venous thromboembolism for users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel

Study period	Oral contraceptive	Cases (n=106)	Controls (n=569)	Adjusted odds ratio (95% CI)*
1 (January 1993 to October 1995)	Levonorgestrel	17	149	1.0
	Third generation	54	247	2.2 (1.1 to 4.3)
2 (January 1996 to December 1999)	Levonorgestrel	25	142	1.0
	Third generation	10	31	2.8 (1.1 to 7.3)
Combined	Levonorgestrel	42	291	1.0
	Third generation	64	278	2.3 (1.3 to 3.9)

*Controls matched to cases by year of birth, index date, and general practice. Estimates adjusted for body mass index, smoking, duration of use of oral contraceptives, and switching.

Additional analyses

To estimate what effect the warning may have had on the incidence of idiopathic venous thromboembolism among users of combined oral contraceptives, we calculated what the expected number of cases in our study population would have been during period 2 if the age specific proportions of the use of either type of oral contraceptive had been the same during both periods. In this calculation we applied age specific incidence for each drug (estimated for the periods combined) to the observed total person time for each age group in period 2 but with the proportion of person time within each age group assigned to either type of oral contraceptive being (hypothetically) the same as that during period 1. For example, we assumed that among woman aged 15-19 years use of third generation oral contraceptives in period 2 accounted for 82% of the 16 100 person years observed (table 1). Under these circumstances we estimated that 44 cases of idiopathic venous thromboembolism would have occurred in the study population (a small fraction of all oral contraceptive users in the United Kingdom) during period 2—that is, 9 (26%) more cases than the 35 that were actually observed.

Discussion

Both the cohort and nested case-control analyses in our study confirm the results of our previous investigation using the General Practice Research Database—namely, that third generation oral contraceptives are associated with around twice the risk of idiopathic venous thromboembolism compared with oral contraceptives with levonorgestrel. The estimated relative risk in the present case-control analysis is higher than the estimated relative incidence from the cohort analysis because the design of the nested case-control study allows for better control of confounding related to cal-

endar time of diagnosis of venous thromboembolism, body mass index, smoking, and duration of oral contraceptive use.

Furthermore, we found that when analyses were adjusted for age, the incidence ratio and the odds ratio for venous thromboembolism comparing the two types of oral contraceptives did not change between the periods before and after the pill scare. This is expected because the risk of venous thromboembolism for each of the two types of oral contraceptive derives from their inherent characteristics (once confounding patient factors are adequately controlled in the study design and analysis). We crudely estimated that about nine (26%) more cases of venous thromboembolism would have occurred during period 2 in our study population (which represents only a small fraction of oral contraceptive users in the United Kingdom) if there had been no shift in the distribution of oral contraceptive use from third generation oral contraceptives to those with levonorgestrel. If the shift in use had been proportionately greater among older women (who have a higher risk of venous thromboembolism), the expected reduction in cases of venous thromboembolism related to oral contraceptive use after the warning would have been greater than observed. The relatively small expected change in the observed number of cases of venous thromboembolism after the warning underscores the inherent limitations of analyses of population trends to detect significant drug effects. It also shows that the attributable risks for venous thromboembolism associated with third generation oral contraceptives, although real, are also small.

Calendar time and time at risk

The relative incidence of venous thromboembolism from 1 January 1993 to October 1995 was similar to that of our original study for January 1991 to November 1994, as were the results from the nested case-control analysis. The relative incidence was also similar for January 1996 to December 1999, after the scare. There was evidence for selective prescribing of third generation oral contraceptives to healthier women, such as those with a lower body mass index, after the scare because part of the warning advised against obese women taking third generation oral contraceptives.

We provided estimates of incidence based on person time at risk. In drug epidemiology, however, such results are relatively crude even with some adjustment for age and calendar time, especially where patterns of drug use change over time. The estimated incidence ratio after adjustment for age for third generation compared with oral contraceptives with levonorgestrel was 1.9. We also performed a nested case-control analysis for the entire study population. This allowed precise control of age, calendar time, and general practice. From this, the adjusted odds ratio estimated for third generation oral contraceptives versus oral contraceptives with levonorgestrel was 2.3, indicating that the estimates based on time at risk did not fully control for calendar time and that adjustment for body mass index, smoking, and duration of use are important for an accurate estimate of effect.

Comparison with other studies

The recent publication by Farmer et al based on data from the General Practice Research Database found no difference in the incidence rates of "idiopathic" venous thromboembolism before and after the scare among women aged 15-49 who were current users of oral contraceptives.[13] They concluded that their data provided evidence against an increased risk of venous thromboembolism associated with third generation oral contraceptives compared with oral contraceptives with levonorgestrel.

Our conclusion differs from that of Farmer et al for several possible reasons. Firstly, we reviewed individually all clinical information available for each woman (blinded to oral contraceptive exposure) to validate the diagnosis of venous thromboembolism and to identify those with an apparent proximate cause of the illness; more than a dozen such causes were identified. For example, five women had undergone knee arthroscopy shortly before being diagnosed with venous thromboembolism. (No such women were in the large group of potential controls.) By contrast, Farmer et al used only an automated computer search to exclude women with a limited number of diagnoses. This procedure would have failed to identify a substantial number of conditions, which we were able to exclude from our study.

The principle that failure to exclude cases with known proximate causes of venous thromboembolism results in substantial bias toward the null is clearly shown by Stolley et al.[16] They performed a hospital based case-control study of oral contraceptives and thrombotic disorders that identified 461 cases, of which only 104 (22%) were considered to be idiopathic after review of the clinical records. The relative risk estimate comparing users of oral contraceptives with non-users was reported as 7.2 (3.9 to 13.0) for idiopathic cases but only 1.9 (1.5 to 2.5) for all cases, including those with apparent proximate causes.

Secondly, our review of individual patient computer records excluded a small number of cases that were not confirmed according to notations by the doctor despite having a diagnostic code listed. If we had obtained complete records from the doctors (including hospital discharge summaries), as in our previous study, we estimate that around an additional 10% of women would have been excluded, leading to a slight underestimate in the present study of the actual relative risk for venous thromboembolism associated with the two types of oral contraceptives.

Thirdly, we restricted our analysis to a comparison of third generation oral contraceptives with oral contraceptives with levonorgestrel, as we had in our previous study. Inclusion of additional oral contraceptives, the use of which increased substantially after the scare, may have obscured the effect of the warning in Farmer et al's study. Information on the risk of venous thromboembolism associated with some of these preparations is uncertain. Indeed, the use of cyproterone acetate has been associated with a higher risk of venous thromboembolism than other products, and the use of oral contraceptives containing cyproterone acetate increased after the scare.[1 17]

Finally, our study reasonably controls for calendar time by matching cases and controls on the date that venous thromboembolism was diagnosed. This is critical in situations where the use of a drug changes rapidly, as has been shown for oral contraceptives after the scare. We also controlled for body mass index and smoking, both of which are risk factors for venous

What is already known on this topic

Third generation oral contraceptives with desogestrel or gestodene have been associated with an increased risk of venous thromboembolism compared with oral contraceptives with levonorgestrel

Since this was reported in October 1995, the use of third generation oral contraceptives has decreased, especially among younger women

What this study adds

Third generation oral contraceptives are associated with a twofold risk of venous thromboembolism compared with oral contraceptives with levonorgestrel

That venous thromboembolism decreased after October 1995 is consistent with the relative risk estimate for third generation oral contraceptives compared with oral contraceptives with levonorgestrel and the observed changes in their use among different age groups

thromboembolism and confound the association between type of oral contraceptive and risk of venous thromboembolism. These factors were not controlled properly in Farmer et al's study. Moreover, their study was not designed directly to estimate the relative risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel, and so the conclusion that there is no difference in risk between the two types of oral contraceptive is not supported by the data. Given the decreased use of third generation oral contraceptives and the increased use of oral contraceptives with levonorgestrel, there must inevitably have been a decrease in the fully adjusted incidence of venous thromboembolism among users of these two types or oral contraceptives after the warning.

The Boston Collaborative Drug Surveillance Program is supported in part by grants from AstraZeneca, Berlex Laboratories, Boehringer Ingelheim Pharmaceuticals, Boots Healthcare International, Bristol-Myers Squibb Pharmaceutical Research Institute, Glaxo Wellcome, Hoffmann-La Roche, Janssen Pharmaceutica Products, L.P., RW Johnson Pharmaceutical Research Institute, McNeil Consumer Products, and Novartis Farmacéutica.

HJ conceived and designed the study and wrote the paper; he will act as guarantor. JAK analysed the data and wrote the paper. CVS analysed the data. SSJ conceived the study and wrote the paper.

Competing interests: The study on use of oral contraceptives based on the General Practice Research Database that was conducted by the Boston Collaborative Drug Surveillance Program in 1996 was funded by NV Organon.

Funding: None.

1 WHO collaborative study of cardiovascular disease and steroid hormone contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995;346:1582-8.
2 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995;346:1589-93.
3 Bleomenkamp KWM, Rosendaal FR, Helmerhorts FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestogen. *Lancet* 1995;346:1593-6.
4 Andersen BS, Olsen J, Nielsen GL, Steffensen FH, Sørensen HT, Baech J, et al. Third-generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism. *Thromb Haemost* 1998;79:23-31.
5 Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999;354:127-8.
6 Vasilakis C, Jick H, Melero-Montes MM. Risk of idiopathic VTE in users of progestogens. *Lancet* 1999;354:1610-1.
7 Vasilakis C, Jick SS, Jick H. The risk of VTE in users of postcoital contraceptive pills. *Contraception* 1999;59:79-83.
8 Farmer RDT, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997;349:83-8.
9 Farmer RDT, Lawrenson RA, Todd J-C, Williams TJ, MacRae KD, Tyrer F, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* 2000;49:580-90.
10 Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169-81.
11 Farley TM, Meirik O, Collins J. Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. *Hum Reprod Update* 1999;5:721-35.
12 Jick SS, Vasilakis C, Jick H. Pregnancies and terminations after 1995 warning about third generation oral contraceptives. *Lancet* 1998;351:1404-5.
13 Farmer RDT, Williams TJ, Simpson EL, Nightingale AL. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. *BMJ* 2000;321:477-9.
14 Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302:766-8.
15 Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. *Pharmacoepidemiol Drug Safety* 1992;1:347-9.
16 Stolley PD, Tonascia JA, Tockman MS, Sartwell PE, Rutledge AH, Jacobs MP. Thrombosis with low-estrogen oral contraceptives. *Am J Epidemiol* 1975;102:197-208.
17 Parkin L, Skegg DCG, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000;355:2133-4.

(Accepted 19 October 2000)

One hundred years ago

A Lady Doctor's Double Victory

A French law court has lately had before it a case presenting some features of special interest to medical practitioners. A lady who holds the degree of Doctor of Medicine of the Faculty of Paris some time ago operated on a young child for abscess of the neck. The operation was successful, but the father declined to pay the bill, which amounted to 400 francs. The lady brought an action, and the defence was that the operation had been badly done, and that the treatment had done more harm than good. These allegations were supported by a certificate from a dentist. The Court, finding its unaided intelligence unequal to the settlement of the dispute, called in the assistance of Professor Brouardel, who is the principal authority on medico-legal matters in France. The eminent Dean of the Faculty of Medicine, after a careful inquiry, gave it as his opinion that the operation had been perfectly successful, and that the treatment had been thoroughly satisfactory. The lady, encouraged by this opinion, straightway brought a further action for damages, on the ground that the defendant had sought to justify his refusal to pay by misrepresentations calculated to injure her in her professional capacity. The Court heard the case argued at full length, because the point, though reasonable, was held to be new, and finally decided in the lady's favour on both counts. The ungrateful parent had therefore not only to pay the bill for attendance, but 50 francs in addition as a solatium to the wounded professional feelings of the lady doctor.
(*BMJ* 1900;ii:1657.)