SURVEY 1

Incidence of arterial disease among oral contraceptive users

ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY*

SUMMARY. The incidence of all initial episodes of arterial disease was investigated in the prospective study of the Royal College of General Practitioners. In general, the findings were consistent with earlier reports, in that the risks of ischaemic heart disease, cerebrovascular disease and peripheral vascular disease were all increased in current users of oral contraceptives. Furthermore, cigarette smoking increased the risk of arterial disease in both pill users and controls, and the risks were greatest in older women.

There were, however, two important new observations, which need confirmation elsewhere. First, the case-fatality rate was increased in women who both smoked and took the pill. Secondly, the risk of cerebrovascular disease remained elevated in former pill users for at least six years after they had stopped oral contraceptives.

Introduction

THE 1981 mortality analysis from the Royal College of General Practitioners' Oral Contraception Study indicated that women who used oral contraceptives had a fourfold increased risk of death from total circulatory diseases (RCGP Oral Contraception Study, 1981). The increased risk was concentrated in pill users aged 35 years and older, especially those who smoked. We noted that it was difficult to determine from mortality data whether an increased risk of circulatory disease in former users represented a real residual effect of oral contraceptives or merely recorded the fatal conclusion of an illness which began while oral contraceptives were still being used. To examine this issue, we have analysed the incidence of all first episodes of circulatory disease, both fatal and non-fatal. This allows us to determine whether or not an illness began during current pill use. In addition, the larger number of recorded events has permitted an evaluation of duration of use and of the interaction of age, smoking status, and oral contraceptive use on the risk of circulatory disease. Finally we examined case-fatality rates for users and non-users of the pill.

Methods

This report includes all events recorded up to December 1979. The study has been described in detail previously (RCGP, 1974). Briefly, during 1968 and 1969, 23,000 women taking oral contraceptives and an equal number of controls (women who have never used the pill) were recruited by 1,400 general practitioners throughout the United Kingdom. Every six months the general practitioners report on the health and oral contraceptive use of women in the continuing study. For each month since they enter the study, women are classified as current-users or former-users of oral contraceptives or as controls. The user groups include women whose pill usage is continuous throughout the period of observation as well as those whose pill usage is intermittent. Thus if a control begins to take the pill, she is classified as a user from the time of the change. To determine the incidence of arterial disease, expressed here as a rate per 1,000 woman-years, the number of reports of initial vascular illnesses (fatal or non-fatal) in each pill-usage group is divided by the calendar months of observation for women in that group. As some women develop two or more different arterial illnesses, the rates for each category of disease include all initial events coded to that category, while the rates for the groups of arterial diseases include only the first event of any of the arterial diseases in that group. For example, a woman who experienced both a heart attack and a stroke would be included in the rates for each disease, but only the first of these events would be counted when total arterial diseases are analysed as a group. Unless otherwise specified, incidence rates are adjusted by indirect standardization for age and parity at the time of diagnosis, and for cigarette consumption and social class at entry into the study, using the total study population as the standard (RCGP, 1974). Because the rates for each disease and for groups of diseases are standard-

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Table 1. Incidence of ischaemic heart disease by oral contraceptive use.

ICD code	Disease	Standardized incidence rate (number of cases)			Relative risk (95 per cent confidence limits)	
		Current-users	Former-users	Controls	Current-users	Former-users
410	Acute myocardial infarction	0.30 (24)	0.19 (18)	0.15 (20)	2.0 (1.1–3.5)*	1.3 (0.6–2.5)
411	Other acute and subacute ischaemic heart disease	0.02 (1)	0.02 (2)	0.01 (2)	1.4 (0.2–10.3)	1.2 (0.1–10.9)
412	Chronic ischaemic heart disease	0.16 (10)	0.25 (25)	0.14 (20)	1.1 (0.6–2.2)	1.8 (0.9–3.3)
413	Angina pectoris	0.32 (21)	0.41 (41)	0.37 (52)	0.9 (0.6–1.4)	1.1 (0.7–1.8)
410–414	All ischaemic heart disease	0.77 (54)	0.63 (62)	0.54 (75)	1.4 (1.0–2.0)*	1.2 (0.8–1.7)

Incidence rates per 1,000 woman-years, standardized for age, parity, social class and smoking status.
Comparison with controls: *$P<0.05$.

Table 2. Incidence of cerebrovascular disease by oral contraceptive use.

ICD code	Cause	Standardized incidence rate (number of cases)			Relative risk (95 per cent confidence limits)	
		Current-users	Former-users	Controls	Current-users	Former-users
430	Subarachnoid haemorrhage	0.14 (11)	0.17 (16)	0.08 (11)	1.7 (0.8–3.8)	2.1 (0.9–4.6)
431	Cerebral haemorrhage	0.03 (2)	0.09 (8)	0.03 (4)	1.1 (0.2–5.1)	3.3 (1.0–11.0)
432	Precerebral stroke	0.00 (0)	0.05 (5)	0.02 (2)	—	3.1 (0.6–15.9)
433	Cerebral thrombosis	0.11 (10)	0.04 (4)	0.00 (0)	—**	—
434	Cerebral embolism	0.08 (6)	0.01 (1)	0.01 (2)	6.0 (1.4–25.6)*	0.9 (0.1–11.1)
435	Transient ischaemic attack	0.10 (8)	0.06 (6)	0.01 (1)	13.8 (2.8–67.9)*	8.7 (1.4–53.2)*
436–438	Other cerebrovascular disease	0.17 (15)	0.17 (15)	0.04 (6)	4.0 (1.7–9.4)**	3.8 (1.6–9.4)**
430–438	All cerebrovascular disease	0.62 (51)	0.50 (46)	0.20 (26)	3.1 (2.0–4.9)**	2.6 (1.6–4.1)**

Incidence rates per 1,000 woman-years, standardized for age, parity, social class, and smoking status.
Comparison with controls: *$P<0.05$, **$P<0.01$.

ized separately, there are small discrepancies between the sum of the individual rates and the rates for the groups.

Periods of pregnancy and associated events have been excluded from these analyses because disease incidence and reporting are modified by pregnancy and there are substantially fewer pregnancies in current-users and former-users (ever-users) than in controls. Statistical methods used are the same as in the 1981 mortality report (Mantel, 1963; RCGP, 1974; Miettinen, 1976). Relative risk (RR) is the ratio of the incidence rate in the user groups to that in controls. When the 95 per cent confidence limits of the relative risk do not include unity, the difference between pill users and controls is statistically significant ($P<0.05$). Case-fatality rates have been calculated as the percentage of women recorded as having a disease who died from that disease.

Since detailed analyses of the association of oral contraceptive use and venous thromboembolism in this cohort have been described elsewhere (RCGP, 1974; RCGP Oral Contraception Study, 1978), this report is confined to the major arterial causes of vascular disease; ischaemic heart disease (International Classification of Diseases (ICD), World Health Organization, 1967) (ICD 410–414), cerebrovascular disease (ICD 430–438) and other diseases of arteries, arterioles, and capillaries (ICD 440–448). The less important condition—chilblains—(ICD 443.2) has been excluded from these analyses, since its frequent occurrence would otherwise dominate the grouping of arterial diseases, and its reporting is more likely to be subject to bias.

Results

The periods of observation in the current-user, the former-user and the control groups were 98,551, 78,142 and 129,593 women-years, respectively.

An analysis of all categories of ischaemic heart disease is given in Table 1. Although the overall risk of ischaemic heart disease in current-users was increased significantly by 40 per cent, the only subcategory for which current-users had a significantly increased relative risk (2.0) was acute myocardial infarction. Former-

Table 3. Cerebrovascular disease incidence in former-users of oral contraceptives by recency of pill use.

		Months since last oral contraceptive used					
	Controls	1–6	7–12	13–24	25–48	49–72	73+
Rate (number of cases)	0.20 (26)	0.69 (6)	0.56 (4)	0.39 (5)	0.44 (9)	0.78 (11)	0.78 (11)
Relative risk	1.0	3.4	2.8	1.9	2.2	3.8	3.8

Rate per 1,000 woman-years, standardized for age.
Relative risk compared with controls.

Table 4. Incidence of peripheral vascular disease by oral contraceptive use.

		Standardized incidence rate (number of cases)			Relative risk (95 per cent confidence limits)	
ICD code	Cause	Current-users	Former-users	Controls	Current-users	Former-users
442	Non-aortic aneurysm	0.00 (0)	0.04 (3)	0.01 (1)	0.0	5.4 (0.7–43.9)
443.0	Raynaud's disease	0.76 (68)	0.53 (41)	0.44 (61)	1.7 (1.2–2.4)**	1.2 (0.8–1.8)
443.8–443.9	Other and unspecified peripheral vascular disease	0.31 (26)	0.32 (28)	0.29 (40)	1.1 (0.7–1.7)	1.1 (0.7–1.9)
444	Arterial embolism and thrombosis	0.08 (8)	0.03 (3)	0.02 (2)	4.4 (1.2–16.1)*	1.5 (0.2–9.1)
445	Gangrene	0.00 (0)	0.01 (1)	0.00 (0)	—	—
446	Polyarteritis nodosa	0.04 (4)	0.02 (2)	0.04 (5)	1.0 (0.3–3.6)	0.5 (0.1–2.7)
447	Other diseases of arteries and arterioles	0.05 (4)	0.02 (2)	0.03 (4)	1.5 (0.4–5.7)	0.7 (0.1–4.2)
448	Diseases of capillaries	0.11 (11)	0.06 (5)	0.06 (8)	1.7 (0.7–4.3)	0.8 (0.3–2.4)
442–448 (excluding 443.2)	Diseases of arteries, arterioles, and capillaries	1.31 (118)	0.90 (73)	0.79 (107)	1.6 (1.3–2.1)**	1.1 (0.8–1.5)
443.2	Chilblains	1.70 (182)	1.26 (91)	1.14 (145)	1.5 (1.2–1.9)**	1.1 (0.9–1.4)

Incidence rates per 1,000 woman-years standardized for age, parity, social class, and smoking status.
Comparison with controls: *$P<0.05$, **$P<0.01$.

users did not have a significantly increased risk of any category of ischaemic heart disease nor for the total.

The pattern of risk of cerebrovascular disease from oral contraceptive usage (Table 2) differs from that for ischaemic heart disease. In total, both current-users and former-users had a significantly increased risk (RR 3.1 and 2.6, respectively). Current-users had a significantly increased risk of cerebral thrombosis, cerebral embolism, transient ischaemic attacks (TIA) and other cerebrovascular diseases. Former-users had significantly increased rates for cerebral thrombosis, TIA, and other cerebrovascular disease, although these rates were lower than in current-users. For subarachnoid haemorrhage, cerebral haemorrhage, and precerebral stroke, former-users had a slightly higher risk than current-users, but these increases could be due to chance.

It is often difficult to distinguish clinically between the various causes of stroke, and for this reason we believe it is unrealistic to present our data categorized as to whether the stroke was haemorrhagic or thrombotic.

A review of the histories of the 46 women who experienced their first episode of cerebrovascular disease as former-users revealed that none had had other arterial diseases diagnosed as current-users of oral contraceptives. However, five of these women (11 per cent) did have hypertension diagnosed when they were taking oral contraceptives. The interval since stopping oral contraception was not clearly related to risk (Table 3), which remained elevated for more than six years after last pill use.

For the peripheral vascular diseases, current-users of the pill had a significantly elevated relative risk of 1.6 (Table 4). The strongest relationship was demonstrated for arterial embolism and thrombosis (ICD 444—RR 4.4). However, the overall increased risk was mainly due to the large number of reported cases of Raynaud's disease, where the significantly increased relative risk was 1.7. Former-users had no increased risk for any peripheral vascular diseases. The rate of reporting of chilblains (ICD 443.2), which we have excluded from

Table 5. Incidence of total arterial diseases by age, smoking status and oral contraceptive use.

Age (years)	Incidence rate (Relative risk compared with non-smoking controls of the same age in parentheses, numbers in italics)					
	Current-users		Former-users		Controls	
	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers
20–24	*6* 0.99 (0.7)	*8* 1.30 (0.9)	*0* 0.00 (0.0)	*1* 0.53 (0.4)	*2* 0.53 (0.4)	*7* 1.48 (1.0)
25–29	*11* 0.90 (1.8)	*15* 1.21 (2.4)*	*2* 0.31 (6.6)	*8* 1.16 (2.3)	*5* 0.52 (1.0)	*7* 0.50 (1.0)
30–34	*24* 1.95 (1.9)*	*19* 1.41 (1.4)	*10* 1.08 (1.0)	*12* 1.15 (1.1)	*16* 1.35 (1.3)	*20* 1.03 (1.0)
35–39	*22* 2.47 (2.5)**	*24* 2.41 (2.4)*	*21* 2.67 (2.7)**	*19* 1.97 (2.0)	*17* 1.55 (1.6)	*18* 1.00 (1.0)
40–44	*35* 6.24 (2.7)**	*17* 2.85 (1.2)	*21* 3.64 (1.6)	*18* 2.66 (1.2)	*20* 2.37 (1.0)	*29* 2.29 (1.0)
45+	*29* 11.82 (4.0)**	*13* 5.76 (1.9)*	*34* 5.89 (2.0)**	*24* 4.46 (1.5)	*37* 5.17 (1.7)*	*26* 2.98 (1.0)
<35	*41* 1.45 (1.6)*	*42* 1.31 (1.5)*	*12* 0.62 (0.7)	*21* 1.05 (1.2)	*23* 0.91 (1.0)	*34* 0.89 (1.0)
35+	*86* 5.75 (3.1)**	*54* 3.30 (1.8)**	*76* 3.70 (2.0)**	*61* 2.74 (1.5)*	*74* 2.62 (1.4)*	*73* 1.85 (1.0)

Rate per 1,000 woman-years.
Comparison with non-smoking controls of same age: *$P<0.05$, **$P<0.01$.

the groupings of arterial diseases, are shown in this table for reference.

In Table 5 the interactions of age, smoking and use of oral contraceptives are examined in relation to total arterial diseases reported. Women aged 35 years and older had appreciably higher rates of arterial disease than did younger women. Cigarette smoking increased the risk for older women in each pill-usage group, but had little effect on women under 35 years old. The greatest risk of arterial disease was in current-users aged 35 years and older who smoked; they had a risk 3.1 times greater than that of their non-smoking controls. The risk of arterial disease in current-users in relation to their duration of current oral contraceptive use is given in Table 6. Neither ischaemic heart disease nor peripheral vascular disease was shown to be associated with duration of pill use. However, in the rates for cerebrovascular disease there was some evidence of a trend, although it was not significant. The risk increased steadily up to eight years of use, but then decreased slightly. We also examined the effect of duration of pill use in continuous users only. The number of arterial diseases reported was substantially smaller and there was no indication of a trend.

Case-fatality rates for ischaemic heart disease and cerebrovascular disease combined are given in Table 7. The case-fatality rates are the percentage of women recorded as having an arterial disease who died of that disease, whether immediately or after a subsequent recurrence. Current-users and former-users of the pill are grouped as ever-users for this analysis, since a woman might have had an initial arterial disease event while a current-user and died later of the disease after having stopped taking the pill. These rates indicate that women who both smoked and had used oral contraceptives had case-fatality rates two to three times greater then those for women in the other groups. Non-smoking oral contraceptive users and control subjects, both smokers and non-smokers, had similar lower case-fatality rates. Peripheral vascular disease was excluded from this analysis because it is so seldom fatal. Only two women died from a peripheral vascular disease; both were ever-users who smoked and the cause of death was mesenteric thrombosis.

Table 6. Incidence of arterial disease by total duration of current oral contraceptive use.

Disease	Controls	Total duration in months of oral contraceptive use				
		1–24	25–48	49–72	73–96	97+
Ischaemic heart disease						
Rate (number of cases)	0.49 (75)	0.93 (12)	0.64 (10)	0.64 (10)	0.66 (9)	0.70 (13)
Relative risk	1.0	1.9	1.3	1.3	1.3	1.4
Cerebrovascular disease						
Rate (number of cases)	0.19 (26)	0.37 (8)	0.49 (10)	0.78 (14)	0.81 (11)	0.51 (8)
Relative risk	1.0	1.9	2.6	4.1	4.3	2.7
Peripheral vascular disease						
Rate (number of cases)	0.79 (107)	1.71 (41)	0.97 (22)	1.32 (25)	0.95 (13)	1.27 (17)
Relative risk	1.0	2.2	1.2	1.7	1.2	1.6
Any arterial disease						
Rate (number of cases)	1.45 (204)	3.00 (61)	2.09 (42)	2.74 (49)	2.42 (33)	2.48 (38)
Relative risk	1.0	2.1	1.4	1.9	1.7	1.7

Incidence rates per 1,000 woman-years, standardized for age, parity, social class and smoking status.
Relative risk compared to controls.

Table 7. Case-fatality rates from ischaemic heart disease and cerebrovascular disease in ever-users of oral contraceptives and controls, by smoking status.

	Case-fatality rate (number of deaths)	
	Ever-users	Controls
Smokers	22.8* (34)	10.9 (6)
Non-smokers	7.5 (7)	6.6 (4)
Total	15.9 (41)	9.0 (10)

Standardized for age.
Standardized for age and smoking.
*Significantly greater than the other three subcategories ($P<0.05$).

Discussion

It is often convenient to consider a single statistic which reflects the association of total circulatory diseases (or subgroups of these diseases) with oral contraceptive use. We believe that these summary statistics have sometimes been misunderstood. Three factors should be clearly appreciated. First it has never been demonstrated that there is an increased risk of all categories of circulatory disease associated with oral contraceptive use. Secondly the risk does not apply uniformly to all users of oral contraceptives, and thirdly there may well be important differences in risk associated with the use of different formulations of the combined oral contraceptives (Inman *et al.*, 1970; RCGP Oral Contraception Study, 1977; Meade *et al.*, 1980; Kay, 1980, 1982). The assessment of specific risks in all three of these areas simultaneously would require a data base much larger than is currently available, so that some grouping of diseases, categories of users or pill brands is essential.

Our present results, while broadly consistent with the mortality findings reported previously (RCGP Oral Contraception Study, 1981), include several important new observations. In general, the relative risks of pill use are lower for the incidence of first events of arterial diseases than for deaths, reflecting a higher case-fatality rate in women who used oral contraceptives than in controls. The raised case-fatality rate in ever-users was almost entirely due to the high rate in oral contraceptive users who also smoked cigarettes. If closer surveillance of pill users had resulted in increased reporting of less severe diseases, lower case-fatality rates would have been expected. That this did not occur suggests that diagnostic and reporting bias is unlikely to have materially affected our observations.

We were unable to detect an increased risk of peripheral vascular diseases in former-users.

Also, as expected from the results of most previous case-control studies (Vessey, 1980) we were unable to detect a significantly increased risk of ischaemic heart disease in these subjects. However, in the report of their large-scale case-control study, Slone and his colleagues (1981) noted a significant trend of acute myocardial infarction in former-users related to the duration of their prior use of oral contraceptives. An increased rate was noted in women aged 40–49 years who had used the pill for five to nine years, and their relative risk was 1.6. After 10 years of use, the relative risk had increased to 2.5. The number of cases reported to us so far is too small to investigate this relationship in our own data.

For cerebrovascular disease, however, there was an increased risk in former users (RR 2.6—95 per cent confidence limits 1.6–4.1). This estimate was based on substantial numbers. The risk remained elevated for more than six years after stopping the pill. A report from the Walnut Creek project (Petitti and Wingerd, 1978) also indicated an increased risk of subarachnoid haemorrhage (RR 5.3) in former-users of oral contra-

ceptives. This estimate, although statistically significant, was based on only five cases among former-users. The largest case-control study of stroke associated with oral contraceptive use was undertaken by the Collaborative Group for the Study of Stroke in Young Women (1973). They reported a ninefold increased risk of thrombotic stroke in current-users, and a twofold increased risk of haemorrhagic stroke. These estimates are compatible with our own observations of current-users, but the Collaborative Group presented no data relating to former-users. In two case-control studies confined to deaths from subarachnoid haemorrhage, Inman (1979) and Thorogood and colleagues (1981) found no significantly increased risk in either current-users or former-users.

Although both require confirmation, the demonstration by Slone and colleagues (1981) of residual effects of oral contraceptive use on the occurrence of myocardial infarction and our own report of a similar effect in relation to cerebrovascular disease demand some consideration of possible mechanisms. It seems unlikely that pill-associated hypertension would take as long as six to 10 years to revert to normal values. It cannot be assumed, however, that the effects of the temporary hypertension on the arterial system and end organs would not persist. The well-documented atherogenic effects of current oral contraceptive use on lipid and carbohydrate metabolism (Bradley *et al.,* 1978; Arntzenius *et al.,* 1978; Wynn *et al.,* 1979; Kay, 1980, 1982) might well be expected to have long-term consequences.

In current-users we were unable to demonstrate an increased risk of ischaemic heart disease or peripheral vascular disease related to duration of use. In contrast, the risk of cerebrovascular disease appeared to increase with increasing duration of pill use up to 96 months of use, but declined with longer use. However, the trend was not statistically significant. No trend with duration of use was apparent when only continuous users were analysed, though the numbers were small. It might be argued that a duration effect, if present, should be more obvious in continuous users than in an analysis of current use in which continuous and intermittent users were combined. However, if the pill has a true residual effect on cerebrovascular disease in former-users, which our findings strongly suggest, it would follow that the risk would remain raised during the intervals between consecutive periods of pill usage and the effect of duration of use would accumulate when intermittent periods of continuous use were added together.

We first reported the significantly increased risk of Raynaud's disease in 1974 (RCGP, 1974) and it has been evident in all our analyses since then. In the Oxford/Family Planning Association cohort study (Vessey *et al.,* 1976) no such excess was reported. However, in that study the diagnoses were based solely on hospital attendances, and since patients with Raynaud's disease rarely require referral to hospital it is likely that only a community-based study could detect the association. In the absence of confirmation from independent studies, we must regard the observation as tentative.

In order to have a sufficient number of cases for investigation of the separate effects of age and cigarette smoking with oral contraceptive use, we were obliged to combine all categories of arterial diseases. This was not entirely a satisfactory solution because of the inclusion of diseases whose severity and association with pill usage varied widely. It is for this reason that we have not quoted absolute risks in this paper, though they may be properly calculated from our data for particular disease categories. The main value of our analysis presented in Table 5 is that it indicates the same pattern of risk increasing with age and with cigarette smoking, as was apparent in our analyses of mortality (RCGP Oral Contraception Study, 1981). These mortality data provide a more realistic basis for modifying clinical practice. Our results are also compatible with those of other workers (Ory, 1977; Jick *et al.,* 1978; Petitti *et al.,* 1979).

Since our data on smoking habits were obtained only on entry to the study in 1968–69, it is likely that there are now some non-smokers among the women we categorized as smokers. As a result, we probably underestimated the effect of smoking on the incidence of arterial disease and on case-fatality rates.

Some bias inherent in our study could account for part of the association between oral contraceptive use and cardiovascular disease morbidity. However, detailed consideration of the likely magnitude of the possible biases in this study (RCGP, 1974; RCGP Oral Contraception Study, 1981; Kay, 1981) and the higher case-fatality rates in ever-users of the pill mentioned earlier, suggest that bias could have only a weak influence on our relative risk estimates.

One potential problem is the heterogeneity of our control group. We have examined the incidence of arterial disease in subgroups of the controls determined by their contraceptive use which was recorded only at recruitment to the study. In those women who reported that they were using no contraceptive—a group who were least likely to be comparable with our oral contraceptive users—the rates of reporting of each group of arterial diseases were consistently slightly higher than in the other control groups. Although those women who reported at entry that they used no contraceptives contributed 29 per cent of the total experience of the control group, 20 per cent of all control subjects later used oral contraceptives and another unknown proportion is likely to have adopted other contraceptive methods. The exclusion of the small group of persistent non-users would diminish, to a small extent, the incidence of arterial disease in the remaining control subjects. This could mean that we might have slightly underestimated the risks associated with oral contraceptive use. Vessey and colleagues (1979) have demonstrated that women who use no contraceptives are an

exceptional group in relation to their risk of breast cancer (they have a lower risk). This observation, like our own, requires confirmation, but consideration of non-contraceptive users is worthy of greater attention in all studies of the associations of oral contraceptives.

Conclusion

In general, our results support the conclusions of the mortality analyses. Current users of oral contraceptives have an increased risk of developing ischaemic heart disease, cerebrovascular disease, and peripheral vascular disease. Furthermore, the risk of arterial disease is minimal in young women who do not smoke.

The two- to threefold increased fatality rate in oral contraceptive users who smoke once again emphasizes the important adverse combined effects of smoking and pill use. However, the increase in case-fatality rate has not been reported previously and requires confirmation.

Our finding of a residual effect of the pill being sustained for more than six years in the incidence of cerebrovascular disease in former-users is worrying, but this also requires confirmation, particularly since other published evidence is inconsistent (Collaborative Group for the Study of Stroke in Young Women, 1973; Petitti and Wingerd, 1978; Inman, 1979; Thorogood *et al.*, 1981).

We could not detect an increased risk of ischaemic heart disease or peripheral vascular disease in former-users, although the data are consistent with the small increase in ischaemic heart disease risk which was reported by Slone and colleagues (1981). Finally, there is a suspicion that the incidence of cerebrovascular disease in current-users is related to duration of oral contraceptive use.

As the necessary data become available, the possible residual effects of oral contraceptives will require much more detailed study.

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