Papers and Originals

Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-bearing Age*

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The use of oral contraceptives in the United Kingdom has increased progressively during the past seven years and it is estimated that between 10 and 15% of married women were regularly using this method of contraception in 1967. During these years numerous accounts have been published in the medical and lay press of individual or small groups of patients who developed thromboembolic disorders while taking oral contraceptives. In the three-and-a-half-year period ending 31 December 1967 the Committee on Safety of Drugs received 1,024 reports of thrombosis or embolism occurring after the use of oral contraceptives or similar preparations. Eighty-eight of these reports referred to a fatal episode.

The Food and Drug Administration (1963) in the U.S.A. reviewed some 350 reports of thrombosis or embolism in women taking Enovid (a mixture of norethynodrel and mestranol, marketed in the United Kingdom as Enavid). As no information was available about the morbidity from these conditions in women not using oral contraceptives, the Food and Drug Administration confined its attention to reports of death. The mortality from thromboembolic disease among users of oral contraceptives was estimated to be 12.1 per million women per year, compared with 8.4 per million in the general population, and this difference in mortality rates was not statistically significant. In 1966 the Food and Drug Administration showed that among the five million women estimated to have been taking oral contraceptives in the United States in 1965, 85 deaths from "idiopathic" thromboembolism would have been expected on the basis of national mortality statistics, whereas only 13 such deaths were reported. It was suggested that physicians in the United States were becoming increasingly fearful of reporting adverse reactions because of the risk of litigation. In the same year the Committee on Safety of Drugs was informed of 19 thromboembolic deaths among the 400,000 women who were estimated to have been using oral contraception in the United Kingdom. Ten of the 19 women had no recognized predisposing conditions.

In November 1965 the Committee on Safety of Drugs (Cahal, 1965) published its findings up to the end of August 1965. In the preceding 12-month period 16 deaths from thromboembolism had been reported among users of oral contraceptives. Thirteen deaths would have been expected on the basis of the Registrar General's statistics, and the Committee did not regard the difference as clear evidence of a thrombogenic effect. They did point out, however, that, whereas only two cases of pulmonary embolism would have been expected, eight had been reported. The Committee therefore decided to enlarge the scope of its investigation to include all deaths from thrombosis or embolism in women of child-bearing age recorded by the Registrars General in England and Wales and Northern Ireland in 1966. Protocols for the investigation were considered by the Committee during the last quarter of 1965, and the study began on 1 January 1966.

During 1966 and early 1967 studies were also undertaken by the Royal College of General Practitioners of patients with thromboembolic disease seen in general practice and by the Medical Research Council's Statistical Research Unit of women admitted to hospital. In April 1967 the results of these two studies, together with those of the Committee on Safety of Drugs, were considered by a subcommittee of the Medical Research Council under the chairmanship of Lord Platt, and a preliminary report to the Council was published in May 1967. Though two of the investigations were at that time incomplete it was concluded that there could be no reasonable doubt that some types of thromboembolic disorder were caused by oral contraceptives. From the preliminary results of the investigation by the Committee on Safety of Drugs it was estimated that the risk of death from thromboembolism among women who used oral contraceptives might amount to an excess of three deaths per 100,000 women per year over the corresponding mortality in non-users.

The Royal College of General Practitioners has published a full report of its investigation elsewhere (Royal College of General Practitioners, 1967), and that of the Medical Research Council's Statistical Research Unit appears elsewhere in this issue (Vessey and Doll, 1968). The present communication describes the final results of the investigation of deaths undertaken by the Committee on Safety of Drugs.

Selection of Deaths for Study

Transcripts of 499 death certificates relating to women aged 20 to 44 who died in England, Wales, and Northern Ireland during 1966 were obtained by special arrangement with the Registrar Generals. They included certificates mentioning thrombosis or embolism of the pulmonary, cerebral, or coronary vessels or other synonymous terms in either the first or second part of the certificate. Certificates relating to deaths attributed to venous thrombosis at peripheral sites but in which pulmonary embolism was not specifically mentioned were also included.[1]

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[1] The great majority of these deaths would be assigned to the following list numbers in the *International Classification of Diseases* (I.C.D.): 332 (cerebral thrombosis and embolism), 420 (arteriosclerotic heart disease, including coronary disease), 463, 464 (phlebitis and thrombophlebitis), 465 (pulmonary embolism and infarction), 466 (other venous embolism and thrombosis). Deaths assigned to list numbers 648 (other complications of pregnancy) 682, 684 (puerperal phlebitis and pulmonary embolism) were not considered.

Eighteen certificates indicated that the thrombosis or embolism was a terminal event in the course of some other fatal disease such as cancer, and these deaths were not further investigated. Forty-nine certificates relating to spinsters were also excluded. Strenuous efforts were made to identify and interview the general practitioners who had cared for the remaining 432 patients. Twenty-seven women, however, were either not registered with any doctor or the coroner, hospital, or local executive council could not identify him. In another 16 instances, though the doctor was identified, arrangements could not be made to interview him within one year of the patient's death. Four doctors refused an interview because they felt they would be unable to be of any assistance.

The remaining 385 deaths were all investigated by the Committee's medical field-officers and a further 51 patients were subsequently excluded for a variety of reasons. One patient's age was found at interview to be 47 (not 41 as certified). Eighteen were widowed, divorced, or separated and living alone (women "living as married" were retained). Investigation showed that thrombosis or embolism was a terminal event in the course of cancer in three patients and in one with subacute bacterial endocarditis; two patients with thrombosis of the superior vena cava were also excluded. Twenty were excluded because the cause of death was not as certified. In a further six patients there was no post-mortem examination and the history and clinical features of the terminal event were too obscure to support the certified cause of death.

The remaining 334 deaths provide the basis for this report. Ninety-five were attributed to pulmonary thrombosis or embolism, 209 to coronary thrombosis or myocardial infarction, and 30 to cerebral thrombosis or embolism.

It is thought that the great majority of deaths from pulmonary embolism and coronary thrombosis that occurred in 1966 have been included in this investigation. The Registrar General for England and Wales, however, has informed us that, because of the widely varying terminology used by certifying physicians, the deaths attributed to cerebral thrombosis or embolism (I.C.D. List No. 332) may not represent all those that occurred from this cause.

Procedure

Thirty-five members of the Committee's staff of medical officers took part in the field work in this study. During the investigation of each death one of them completed a questionary as fully as possible with the aid of the general practitioner and any other doctors who had attended the patient during her terminal illness. Since the general practitioner's records had usually been returned to the local executive council after the patient's death, he was asked to retrieve them before the medical officer called to interview him. These major sources of information were often supplemented by hospital case notes, family planning clinic records, post-mortem reports, and court depositions supplied by a coroner. As a matter of policy no attempt was made to obtain information direct from the patient's relatives.

The deaths of eight users of oral contraceptives had been notified independently to the Committee before the summaries of the corresponding death certificates had been received. This information was withheld from the field-officers to avoid possible bias.

The questionaries asked about the patient's (1) age and marital status, (2) obstetrical, gynaecological, medical, and family histories, and (3) terminal illness and post-mortem findings. Questions were also included about any drugs, including oral contraceptives, which had been taken by the patient at the onset or at any time during the six months preceding the terminal illness. Check-lists of the proprietary names of the various preparations used as oral contraceptives were provided.

In addition to providing details concerning the fatal case each general practitioner was also requested to give information for comparative purposes about the age, marital status, parity, and current use of oral contraceptives of certain other women in his practice. It was thought that, since considerable demands had already been made on his time, close age and parity matching between the dead woman and these control subjects would not be possible. An extensive search of the practice records would often be involved, in particular when the woman who had died had borne many children.

The procedure for obtaining controls was therefore very simple. Each doctor was asked to locate in his files the position which would have been occupied by the late patient's records and which was usually still occupied by records relating to other members of her family. Moving first forwards and then backwards from that position, the doctor selected the first two sets of case notes encountered relating to women aged 15 to 44 years. Irrespective of whether or not the doctor had all the necessary information about these subjects, they were accepted as controls.

Subsequent experience showed that this procedure of selecting two controls at each interview was yielding too few subjects of high parity. Therefore for interviews concerning patients who died after 1 July 1966 four to six controls were obtained at each interview and the selection was also limited to women who were married.

In this way information about 1,133 married control subjects aged 20 to 44 years was collected.[2] Of these, 17 were known to be pregnant, 28 were of unknown parity, and there was no record of whether or not a further 90 were using oral contraceptives. These 135 controls were omitted from the analysis.

Assessment

Many conditions such as prolonged immobility, recent surgery, hypertension, and diabetes mellitus must be regarded as predisposing towards some types of thromboembolic disease. Each case history was therefore carefully examined for evidence of the presence of these or other conditions which might have contributed to the terminal illness. On receipt of each completed questionary the data concerning the patient's age, parity, and drug history were separated from the remaining information to avoid any bias in the subsequent assessment. Each case history was then considered independently by three assessors and placed in one of the following categories:

Class A.—Patients with no known predisposing conditions.

Class B.—Patients with known predisposing conditions who were neither pregnant nor in the puerperium.

Class C.—Patients who were pregnant or had been delivered during the month before the onset of the terminal episode.

At subsequent conferences it was found that major disagreement between the three assessors was unusual, and in every case it was possible to reach agreement on classification.

Results in Control Subjects

Table I shows the pattern of use of oral contraceptives by the 998 control subjects retained in the analysis, classified by age and parity. Among women aged 20 to 24 years there was a steady rise in the proportion using oral contraceptives from 9% of those who had never borne children to 44% of those who had borne three or more. The pattern was similar for women aged 25–34 years, though at a slightly lower level throughout the parity range. Among those aged 35–44 none of the 40 nulliparous women were using oral contraceptives

[2] Controls aged 15–19 years were discarded, as none of the deaths studied occurred in that age group.

and the proportion among those who had borne fewer than four children was uniformly low.

TABLE I.—*Use of Oral Contraceptives by Control Subjects in Relation to Age and Parity*

Parity	Age 20–24		Age 25–34		Age 35–44		All Ages	
	No.*	%†	No.*	%†	No.*	%†	No.*	%†
0	45	8·9	52	5·8	40	0·0	137	5·1
1	46	15·2	91	8·8	88	10·2	225	10·7
2	32	34·4	172	25·0	141	9·9	345	19·7
3	9	43·8	85	30·1	68	11·8	162	22·8
4 or more	7		52	28·8	70	22·9	129	27·1
All parities	139	20·9	452	21·0	407	11·5	998	17·1

* Number of women studied.
† Percentage of women using oral contraceptives.

Results in Fatal Cases

Twenty-five deaths occurred during pregnancy or the puerperium (class C). These are not considered in this communication. Fifty-three (17.2%) of the remaining 309 patients were using oral contraceptives at the onset of the terminal episode. Five of these 53 women had obtained their oral contraceptives from a family planning clinic, three from a gynaecologist, 39 from their general practitioner, and six from another general practitioner when their own had declined to prescribe for them.

Pulmonary Embolism (77 deaths)

Class A.—Of the 26 patients in this category, only one did not have a post-mortem examination. The standard of diagnostic accuracy is therefore high in this class. Nineteen of the death certificates were signed by a coroner, four by a hospital doctor, and the remaining three by a general practitioner after post-mortem examination. Sixteen of these patients had been taking oral contraceptives at the onset of the fatal illness (Table II). The corresponding number predicted from the experience of control women of like age and parity is only 4.2[3] and this great disparity in the use of oral contraceptives between the dead women and the control women is statistically highly significant (P<0.001). Table III shows that the excess of users of oral contraceptives among those women who died was present within broad age and parity groups. No women in this class had been taking any other type of sex-hormone preparation before becoming fatally ill.

Class B.—Fifty-one patients who had the following predisposing conditions were allocated to class B: recent surgery (17), prolonged immobilization due to a variety of medical conditions (12), previous thromboembolism (9), cardiovascular disease (8), blood disease (3), and diabetes mellitus (2). Even though many patients had suffered prolonged ill-health, post-mortem examinations had been carried out on 43 of them and 20 death certificates were signed by a coroner. It was uncertain whether two of these patients had been using oral contraceptives at the onset of the terminal episode, but nine of the remaining 49 had been doing so (Table II). The corresponding expected number calculated from the control data is slightly smaller (6.8), but the difference between the experience of the study and control groups is not statistically significant.

[3] Throughout this report the expected numbers of women using oral contraceptives have been calculated from the data shown for control subjects in Table I. In making any calculation the first step was to classify the dead women, irrespective of known oral contraceptive use, into the same age and parity groups as those shown in Table I. The expected number of oral contraceptive users in each cell of the table was obtained by multiplying the cell total by the corresponding percentage in Table I and dividing the result by 100. The individual cell expected numbers were then summed to give the overall expected number.

For tests of significance, the control data shown in Table I were reclassified in nine subgroups by combining adjacent cells containing similar percentages, and the method of Mantel and Haenszel (1959) was applied.

If classes A and B are combined a highly significant excess of oral contraceptive users among the women who died is still found (Table II, P<0.001). Errors in the assessment of predisposing conditions cannot therefore be responsible for the strong association between death from pulmonary embolism and the use of oral contraceptives.

TABLE II.—*Use of Oral Contraceptives by Women Dying from Pulmonary Embolism. Numbers Expected from Experience of Control Women of Similar Age and Parity are Shown in Parentheses*

Predisposing Conditions	No. of Deaths Among		
	Users of Oral Contraceptives	Non-users of Oral Contraceptives	All Women
Absent (class A)	16 (4·2)	10 (21·8)	26
Present (class B)	9 (6·8)	40 (42·2)	49*
Total (classes A and B)	25 (11·0)	50 (64·0)	75

* Two patients whose contraceptive practice was unknown omitted from this category.

TABLE III.—*Use of Oral Contraceptives by Women Dying from Pulmonary Embolism Without Known Predisposing Cause (Class A) by Age and Parity. Numbers Expected from Experience of Control Women Shown in Parentheses*

Age	Parity	No. of Deaths Among		
		Users of Oral Contraceptives	Non-users of Oral Contraceptives	All Women
20–34	0–3	4 (1·5)	3 (5·5)	7
	4+	2 (0·6)	0 (1·4)	2
	Total	6 (2·1)	3 (6·9)	9
35–44	0–3	6 (1·0)	6 (11·0)	12
	4+	4 (1·1)	1 (3·9)	5
	Total	10 (2·1)	7 (14·9)	17
All ages	0–3	10 (2·5)	9 (16·5)	19
	4+	6 (1·7)	1 (5·3)	7
	Total	16 (4·2)	10 (21·8)	26

Coronary Thrombosis (205 deaths)

Class A.—Post-mortem examinations were carried out in 74 of the 89 patients (83%) in this class, and diagnostic accuracy is therefore likely to be high. Sixty-one death certificates were signed by a coroner, 14 by a hospital doctor, and 14 by a general practitioner. Details of oral contraceptive use or parity were unknown for five patients, who have been omitted from the analysis shown in Table IV. Of the remaining 84 deaths 18 occurred in users of oral contraceptives while only 11.4 such deaths would have been expected from the experience of the control series. This difference does not, however, quite attain statistical significance (P=0.06). Fifteen patients in this class were known to have been obese. None had being using oral contraceptives. The assessors were reluctant to include obesity as a predisposing condition, because body weight and height had not been recorded for all the women who died and for none of the controls. If, however, these patients are omitted from class A the excess of oral contraceptive users among the remainder attains statistical significance (P<0.01). Examination of the results within the age and parity groups shown in

TABLE IV.—*Use of Oral Contraceptives by Women Dying from Coronary Thrombosis. Numbers Expected from Experience of Control Women Shown in Parentheses*

Predisposing Conditions	No. of Deaths Among		
	Users of Oral Contraceptives	Non-users of Oral Contraceptives	All Women
Absent (class A)	18 (11·4)	66 (72·6)	84*
Present (class B)	5 (12·6)	105 (97·4)	110†
Total (classes A and B) ..	23 (24·0)	171 (170·0)	194

* Five patients omitted from this category—3 whose contraceptive practice was unknown and 2 whose parity was unknown (non-users).
† Six patients omitted from this category—5 whose contraceptive practice was unknown and 1 whose parity was unknown (non-user).

Table V reveals a significant excess of users of oral contraceptives only among young women of low parity.

TABLE V.—*Use of Oral Contraceptives by Women Dying from Coronary Thrombosis Without Known Predisposing Cause (Class A) by Age and Parity. Numbers Expected from Experience of Control Women Shown in Parentheses*

Age	Parity	No. of Deaths Among		
		Users of Oral Contraceptives	Non-users of Oral Contraceptives	All Women
20–34	0–3	7 (2·7)	6 (10·3)	13
	4+	0 (0·6)	2 (1·4)	2
	Total	7 (3·3)	8 (11·7)	15
35–44	0–3	8 (4·5)	45 (48·5)	53
	4+	3 (3·6)	13 (12·4)	16
	Total	11 (8·1)	58 (60·9)	69
All ages	0–3	15 (7·2)	51 (58·8)	66
	4+	3 (4·2)	15 (13·8)	18
	Total	18 (11·4)	66 (72·6)	84

It should also be noted that five women in class A had been using sex-hormone preparations other than oral contraceptives before the onset of the fatal illness. Two had taken Metrulen-M (a substance identical to Ovulen, but normally prescribed for gynaecological disorders); one had taken ethinyloestradiol; one had taken Primolut-N (norethisterone); and one had taken Duphaston (dydrogesterone). The frequency of use of these substances in the control series is, however, unknown, and they have therefore been discounted in the above analysis.

Class B.—The 116 patients who had the following predisposing conditions were allocated to class B: hypertension (46), previous stroke or coronary thrombosis (19), diabetes mellitus (12), long-standing angina pectoris (8) rheumatic heart disease (7), hypercholesterolaemia (6), and various other conditions (18). A post-mortem examination was made in 70 cases (60%). Fifty-three certificates were signed by a coroner, 25 by a general practitioner, and 38 by a hospital doctor. Nothing was known about the use of oral contraceptives by five patients and the parity of another was not recorded. Of the remaining 110 only five had been using oral contraceptives, whereas the number expected from the control experience is 12.6 (Table IV). This difference is just statistically significant ($P=0.05$), and may be due to the reluctance of doctors to prescribe oral contraceptives for women suffering from serious chronic diseases or to a reduced demand for them by such women.

In contrast to the results for pulmonary embolism, if classes A and B are combined there is close agreement between the observed number of women who had been using oral contraceptives and the number expected (Table IV).

Cerebral Thrombosis (27 deaths)

Class A.—The diagnosis was confirmed at post-mortem examination in 7 of the 10 patients in this category, and in two others internal carotid occlusion was demonstrated angiographically. Nine certificates were signed by a hospital doctor and one by a coroner. Five of the 10 patients had been using oral contraceptives at the onset of their terminal illness, while only 1.5 would be expected to have been doing so from the experience of the control series (Table VI). Even though the number of women dying from cerebral thrombosis is so small, this difference between the two groups is statistically significant ($P<0.01$). The data are too few for detailed examination by age and parity, but it is noteworthy that five of the six women under 40 years had been using oral contraceptives, while none of the four over 40 years had taken them.

TABLE VI.—*Use of Oral Contraceptives by Women Dying from Cerebral Thrombosis. Numbers Expected from Experience of Control Women Shown in Parentheses*

Predisposing Conditions	No. of Deaths Among		
	Users of Oral Contraceptives	Non-users of Oral Contraceptives	All Women
Absent (class A)	5 (1·5)	5 (8·5)	10
Present (class B)	0 (1·5)	16 (14·5)	16*
Total (classes A and B)	5 (3·0)	21 (23·0)	26

* One patient omitted from this category whose parity was unknown (non-user).

Class B.—The principal predisposing conditions which caused 17 of the deaths from cerebral thrombosis or embolism to be allocated to class B were as follows: hypertension (9), previous cerebrovascular accident (2), recent surgery (2), and other conditions (4). A post-mortem examination had been performed on only seven of these patients and only two death certificates were signed by a coroner. Details of the use of oral contraceptives were not available for one patient, but none of the remaining 16 had taken them (Table VI). One patient had been taking Metrulen-M for a week only before her death.

When classes A and B are combined there is a small excess of users of oral contraceptives among the women who died.

Oral Contraceptive Preparations used by Women who Died

Of the 39 women allocated to class A in all three diagnostic groups who had been taking oral contraceptives at the onset of the terminal illness, the preparation then in use was ascertained for 34. Similar information was not available for the control subjects, so a comparison was made with national sales statistics provided for the year 1966 by Intercontinental Medical Statistics Limited. There was no suggestion that the risk of thromboembolism was associated with any particular oestrogen-progestogen combination.

The duration of treatment had been recorded for 35 of these 39 patients. There was some suggestion that those who died from coronary thrombosis had been using oral contraceptives rather longer on the average (mean 16 months) than those who died from pulmonary embolism (mean 12 months) or cerebral thrombosis (mean 6 months).

Discussion

The frequency of thromboembolic disorders is inversely related to their severity. Superficial venous thrombosis in young women is a common condition. Deep venous thrombosis and pulmonary embolism are much less common and death from thrombosis is comparatively rare. In the investigation carried out by the Royal College of General Practitioners (1967) two-thirds of the patients had suffered only from superficial venous thrombosis and no conclusions can be drawn about the more serious conditions.

The serious forms of thromboembolic disease such as deep venous thrombosis or pulmonary embolism leading to hospital admission can be studied more easily. Objective diagnostic criteria can be applied and the diagnosis can often be supported by special investigation. The work of Vessey and Doll (1968) has shown that conclusions can be drawn from the investigation of a comparatively small number of carefully selected patients who have been treated in hospital.

The present study was initiated in direct response to the receipt of "random" reports to the Committee on Safety of Drugs of episodes of thromboembolic disease in women using oral contraceptives. At the time the study began there was no important difference between the number of reported deaths and the number expected on the basis of national mortality statistics. However, the hypothesis that there was no relation between the use of oral contraceptives and fatal thrombosis depended on the assumption that there had been almost complete reporting of thromboembolic deaths. That this assumption is untenable has now been demonstrated.

In spite of widespread publicity in both the medical and the lay press, particularly in 1965, only 8 of the 53 deaths of known users of oral contraceptives in the present study were reported

independently to the Committee on Safety of Drugs. Only two of these eight deaths were reported by the patient's general practitioner, though he was almost invariably aware that she had been taking oral contraceptives.

Before attempting to draw any firm conclusions from the other results of this investigation it is important to consider the sources of bias which might have influenced the data on which they are based.

Possible Sources of Bias in Fatal Cases

Forty-seven patients were excluded from the study because efforts to secure an interview with the general practitioner failed for one reason or another. This number represents about 11% of the total number of deaths which would have been investigated had a complete follow-up been possible. We can, however, see no reason why this should have introduced any bias, since control patients were selected only from the practice lists of co-operating doctors.

Apart from these 47 patients there can be little doubt that as a result of incorrect or incomplete death certification an unknown additional number of deaths from thromboembolism were never considered at any stage. Omissions of this sort, however, would be most likely to involve deaths where predisposing conditions were present and the certifier would have a choice of items to enter on the death certificate.

Since 104 (83%) of the 125 women included in class A had had a post-mortem examination, positive diagnostic errors are unlikely to have had much influence in this study.

Incorrect allocation of deaths to classes A or B cannot be responsible for the strong association demonstrated between oral contraception and pulmonary embolism. It is present when all patients dying from that condition are considered as well as when class A patients are considered alone. The same does not apply to deaths from coronary or cerebral thrombosis, but the assessment of predisposing conditions was made without the disclosure of contraceptive practices, and the assessors had no difficulty in making the great majority of decisions.

Possible Sources of Bias in Control Subjects

A number of criticisms can be directed at the control series. Of these much the most important is that information concerning the contraceptive habits of the control women was sought *at the time of interview* with the general practitioner, and this was usually three to nine months after the corresponding patient with thromboembolism had died. As the use of oral contraceptives has been steadily increasing, this must have produced an overestimate of oral contraceptive use in the controls. Moreover, the fact that the number of controls chosen at each interview was increased in the latter half of the study will have accentuated this bias.

Another difficulty is that inquiries about the contraceptive practices of the women who died were sometimes made in hospitals and family planning clinics as well as from general practitioners, whereas the last-mentioned were the only source of information about the practices of the controls. This source of bias has, however, been of little consequence, since the general practitioner was unaware that a dead patient had been taking oral contraceptives on only two occasions. Both these patients died from pulmonary embolism (class A). If they are excluded from the study the results so far described are not materially affected.

Bias may also have been introduced because the proportion of women for whom it was not possible to obtain definite information about the use of oral contraceptives was larger among the controls (90 out of 1,133) than among those who died (11 out of 334). In the present analysis all these women have been omitted. It is improbable that many were using oral contraceptives because the only important source of prescriptions other than the general practitioner himself is the Family Planing Association, and that organization customarily informs family doctors about any patients for whom oral contraceptives are prescribed. This factor will again have led to overestimation of oral contraceptive use among the controls.

The control group will also have included an unknown number of women for whom oral contraceptives had been prescribed but who abandoned their use without informing their doctor either because of side-effects or desire for a pregnancy. Since only 17 of nearly a thousand controls were stated by their doctor to be pregnant, it is likely that some others had either not reported this fact to their doctor or were unaware of it themselves.

A final difficulty arises from the fact that no information was obtained about the health of the control women. Comparisons between the previously healthy women who died and the controls are thus biased by the inclusion of some controls who would have been omitted had it been possible to apply to them the same criteria. We do not believe that this is likely to have led to an appreciable bias, since only a small proportion of the general married female population aged 20–44 years (probably less than 10%) would be expected to have been suffering from one or more of the predisposing conditions of importance in this investigation.

We conclude, therefore, that most of the sources of bias have tended to produce an overestimation of the number of controls using oral contraceptives, and this conclusion is supported by a comparison of the control data with information from other independent sources.

Estimates of Oral Contraceptive Use

At the time the present investigation began, oral contraceptives were not available for prescription on form E.C.10 except when required for purposes other than conception control. It has therefore not been possible to monitor their use through the N.H.S. Pricing Bureau.

Data provided by Intercontinental Medical Statistics Limited represent purchases by patients from chemists but do not include purchases from dispensing doctors, family planning clinics, etc. For the year 1966 oral contraceptives representing about 480,000 woman-years' supply were purchased in this way in England, Wales, and Northern Ireland, and for 1967 the corresponding figure, based on the first half-year's data only, is estimated at about 625,000. These estimates of use do not, of course, correspond to the actual number of women taking oral contraceptives during a year, since many will have started or stopped treatment during that time. They can, none the less, be regarded as estimates of total exposure to the preparations.

Further independent data supplied by the Association of the British Pharmaceutical Industry, which are based on the manufacturers' total sales and free sample distribution, indicate an estimated supply of oral contraceptives in 1966 in England, Wales, and Northern Ireland equivalent to about 700,000 woman-years. If we assume that about 15% of women using oral contraceptives obtained them in 1966 from family planning clinics[4] (H. Hill, personal communication, 1967) and allow some margin for unsold stocks, free samples, prescriptions for purposes other than contraception, etc., the two sets of data show reasonable agreement.

The estimated non-pregnant married female population of England, Wales, and Northern Ireland aged 20–44 in 1966 was approximately 5.7 million. No estimate of the use of oral contraceptives by single women or by women under the age of 20 or over the age of 44 is available, but it is believed to be a very

[4] Among the dead patients in this study 5 out of 53 (9.5%) had obtained oral contraceptives from the Family Planning Association.

small proportion of the total. The Association of the British Pharmaceutical Industry data thus indicate that during 1966 oral contraceptives were taken during 12–13% of these 5.7 million woman-years. This figure is slightly lower than that of 15.3% calculated from the data collected for control subjects during interviews conducted in 1966. In 1967 the Association of the British Pharmaceutical Industry estimates for the first half of the year correspond to an annual supply of about 900,000 woman-years, or 15–16% of 5.7 million woman-years. The corresponding percentage for the control data collected during 1967 is again higher at 18.9.

Estimates of Mortality Attributable to Oral Contraceptives

From the description of the results and the discussion of the reliability of the data it is clear that a strong association between the use of oral contraceptives and death from pulmonary embolism in previously healthy women has been established. A similar result has been found in an investigation of non-fatal episodes of venous thromboembolism (Vessey and Doll, 1968), and since we cannot envisage any common factor which might have been responsible for the production of the disease and the use of oral contraceptives, our conclusion is that the association is one of cause and effect.

The evidence for an association with death from cerebral thrombosis is also strong, though the data are few. Support is provided by the findings in other studies (Illis *et al.*, 1965 ; Bickerstaff and Holmes, 1967 ; Vessey and Doll, 1968), and it seems reasonable to conclude that a small but definite risk exists.

The situation is less well defined for coronary thrombosis. Considered overall, no significant association has been found between death from this disease and the use of oral contraceptives, a finding in keeping with that of Vessey and Doll (1968), though in that study there were few patients with coronary disease and in some the diagnosis was uncertain. There are, however, some subgroups in the present study among whom a significant association between oral contraception and death from coronary thrombosis has been found, in particular among young women of low parity. The work of Wynn and Doar (1966, and of Wynn *et al.* (1966) has shown that a proportion of women using oral contraceptives develop abnormalities of carbohydrate and lipid metabolism similar to those of steroid diabetes. The association between diabetes mellitus and coronary thrombosis is well established.

It is important to estimate the risk of a fatal outcome to oral contraception and also to identify any groups of women at special risk. Unfortunately this investigation can provide no information about the risk among women suffering from predisposing conditions. It is, however, possible to form some estimate of the risk for women without predisposing conditions in two broad age groups, and this has been done in Table VII.

TABLE VII.—*Estimates of Risk of Death from Pulmonary Embolism or Cerebral Thrombosis in Users and Non-users of Oral Contraceptives Compared with Risk of Death from Certain Other Causes*

	Age in Years	
	20–34	35–44
Estimated annual death rate per 100,000 healthy married non-pregnant women from pulmonary cerebral thrombo-embolism:		
Users of oral contraceptives	1·5	3·9
Non-users of oral contraceptives	0·2	0·5
* Annual death rate per 100,000 total female population from:		
Cancer	13·7	70·1
Motor accidents	4·9	3·9
All causes	60·1	170·5
* Death rate per 100,000 maternities from:		
Complications of pregnancy (List Nos. 640–649)	7·5	13·8
Abortion (List Nos. 650–652)	5·6	10·4
Complications of delivery (List Nos. 660–678)	7·1	26·5
Complications of the puerperium:		
Phlebitis, thrombosis and embolism (List Nos. 682–684)	1·3	2·3
Other complications (List Nos. 681, 683, 685–689)	1·3	4·6
All risks of pregnancy, delivery, and puerperium	22·8	57·6

* Registrar General for England and Wales for the year 1966.

When an adverse reaction to a drug is itself a spontaneously occurring disorder with a "natural" incidence it is important to distinguish between the relative and absolute risks of the drug. The results shown in Table VII suggest that, irrespective of age, the risk of death from pulmonary embolism or cerebral thrombosis was increased seven to eight times in users of oral contraceptives. In absolute terms, however, the attributable mortality was substantially lower among those aged 20–34 than among those aged 35–44, there being an excess of 1.3 and 3.4 deaths per 100,000 users per annum respectively.

These estimates exclude deaths from coronary thrombosis because the evidence that oral contraceptives can cause this disease is weaker than that for pulmonary embolism and cerebral thrombosis. If it is thought justifiable to include deaths from coronary thrombosis the mortality attributable to oral contraceptives may be recalculated as 2.2 per 100,000 users per annum for women aged 20–34 and 4.5 per 100,000 users per annum for women aged 35–44.

The risks associated with the use of oral contraceptives in these two age groups have been compared in Table VII with some other risks to which women of similar age are exposed. It will be seen that, although the mortality attributable to oral contraceptives in women aged 35–44 is greater than that in younger women, the general mortality, including that associated with child-bearing, is also substantially increased in this age group. If the risk attributable to the use of oral contraceptives is expressed in terms of the total risk of death, it can be seen that in both age groups this risk amounts to about 2% of the total mortality.

It is very difficult to make any direct comparison between the thromboembolic risks of child-bearing and those of oral contraception. The Registrar General's statistics are known to underestimate the number of deaths in the puerperium attributable to venous thrombosis and pulmonary embolism, and deaths from these conditions occurring during pregnancy are not separately categorized. On the other hand, some deaths from thromboembolism during pregnancy or the puerperium are associated with predisposing factors that are unrelated to child-bearing. Also, in making all the estimates already described of the risks associated with oral contraception, it was assumed that the experience of our control series adequately represented that of the corresponding population of England, Wales, and Northern Ireland in 1966. There is good reason for thinking that this assumption may be incorrect. Thus 17.1% of the control women were using oral contraceptives, and this percentage is equivalent to about 975,000 woman-years of use in the general population. This estimate is almost 40% higher than that provided by the Association of the British Pharmaceutical Industry for the total distribution of oral contraceptives in 1966. It therefore seems very likely that we have underestimated the mortality attributable to oral contraceptives by a corresponding amount.

On balance, it seems reasonable to conclude that the risk of death from pulmonary embolism during one year's treatment with oral contraceptives is of the same order as the comparable risk of bearing one child. In assessing the risks, however, it is important to remember that women in the United Kingdom give birth, on average, to only two or three children in their lifetime, that other methods of contraception are reasonably effective, and that birth control may be practised during most of a woman's child-bearing years.

Summary

Inquiries were made by the medical field-officers of the Committee on Safety of Drugs about the use of oral contraceptives by 385 married women aged 20–44 who died during 1966 in England, Wales, and Northern Ireland from thrombosis or embolism of the pulmonary, cerebral, or coronary vessels. For comparison, information about the use of oral contracep-

tives was also obtained for a control series of women drawn from the same doctors' practices as those in which the fatalities occurred.

A strong relation was found between the use of oral contraceptives and death from pulmonary embolism or cerebral thrombosis in the absence of predisposing conditions. The mortality from these two diseases attributable to the use of oral contraceptives by healthy women was estimated at 1.3 per 100,000 users aged 20–34 and 3.4 per 100,000 users aged 35–44 per annum.

The women who died from coronary thrombosis in the absence of predisposing conditions had been using oral contraceptives more frequently than would have been expected from the experience of the control group, but the difference did not quite attain statistical significance, and the existence of a definite association is regarded as not proved. If it is considered justifiable to include deaths from coronary thrombosis in the above estimates of attributable mortality, they may be recalculated as 2.2 and 4.5 per 100,000 users per annum for women aged 20–34 and 35–44 respectively, figures which agree closely with the estimate of risk given by the Medical Research Council (1967) in its preliminary report. It is probable, however, that all these estimates of risk are too low because information from independent sources indicates that our control data substantially overestimated the use of oral contraceptives by the general population in 1966.

No evidence was found that the risk of thromboembolism was associated with the use of any particular oral contraceptive formulation.

Only 15% of the deaths of women who were found to have been using oral contraceptives were reported independently to the Committee on Safety of Drugs.

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Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease

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In May 1967 a subcommittee of the Medical Research Council reviewed the preliminary results of three inquiries into the risks of thromboembolic disease in women taking oral contraceptives. One study concerned episodes of thromboembolic disease seen in general practice, and the final results have been reported by the Royal College of General Practitioners (1967). Another concerned women who died of thromboembolic disease in England, Wales, and Northern Ireland in 1966; it was undertaken by the Committee on Safety of Drugs, the full results being reported elsewhere in this issue by Inman and Vessey (1968). The third, which was carried out by the Medical Research Council's Statistical Research Unit, concerned women admitted to hospital for deep vein thrombosis and pulmonary embolism. We now report the final results of this study, based on more than double the number of patients, and add some new data on women with cerebral or coronary thrombosis.

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I. Deep Vein Thrombosis and Pulmonary Embolism

Method

Co-operation was sought and obtained from the medical staff of the 19 general hospitals of more than 300 beds situated in the catchment area of the North-West Metropolitan Regional Hospital Board, which maintained a sufficiently detailed nosological index. At each hospital the index was searched and the case notes were reviewed relating to all women who (1) had been admitted to hospital in 1964–6; (2) were aged 16 to 40 years inclusive; and (3) had been diagnosed as suffering from a condition coded Nos. 463–466 in the *International Classification of Diseases* (World Health Organization, 1957)[1]—that is, from phlebitis, thrombophlebitis, thrombosis, or embolism in any vein except the cerebral, coronary, hepatic, and mesenteric veins; pulmonary embolism or infarction.

[1] Or the equivalent numbers at the four hospitals which used other coding systems.