A study was made of hospitalized female patients aged 15-44 who developed pulmonary embolism or venous thrombosis after trauma or surgery. Matched with controls, information was collected on the prior use of oral contraceptives. Findings support previous studies indicating a relationship between thromboembolism and the use of oral contraceptives.

Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection

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Introduction

Four retrospective studies have shown that oral contraceptives are related to the occurrence of thromboembolic disease in healthy women taking this medication.[1-4] Estrogenic substances have also been shown to increase the risk of these conditions when used to suppress lactation post-partum[5,6] and when used as treatment for prostatic carcinoma or coronary artery disease in men.[7-9] These three studies with men were randomized experimental trials. Three studies in Great Britain and the United States have suggested that mortality of young women from thromboembolic diseases is increasing at a faster rate than for other age-sex groups.[10-12] Vessey and others[13] recently evaluated the risk of thromboembolic complications related to use of oral contraception by women undergoing surgery. In this study 30 women with post-surgical thromboembolism were compared with 60 matched controls who had also undergone surgery, but without complications. Twelve (40%) of the cases and nine (15%) of the controls had been taking oral contraceptives in the month preceding their operations, yielding a relative risk of 3.8.

In the pilot stage of data collection for a case-control study of women hospitalized for thromboembolic disease,[4] only a fraction of the cases being collected were acceptable for study because of the requirement that they be free of predisposing conditions or a history of recent trauma. Furthermore, major problems were anticipated in the analysis of non-idiopathic cases. It would be impossible to match cases with controls, disease for disease. There was a general lack of knowledge concerning risk of thromboembolism for women who had had such conditions previously, who were in various stages of chronic illness, or who had undergone surgery, trauma, or merely prolonged immobilization in a cramped position. In addition, no information was available on the likelihood that the above situations would lead a women to use or not use oral contraception. On the other hand, analysis of cases in which the reason for admission was not the thromboembolic event itself would be useful. Such an analysis would be less subject to the possible bias resulting from a physician's being more likely to admit a woman to the hospital for thromboembolic disease if she were using oral contraception than if she were not.

An analysis of non-idiopathic thromboembolism would help determine whether surgery for a user of oral contraceptives was more hazardous than for a nonuser and shed light on any additional risk for women already in high-risk groups. We decided for ease of matching to use as cases women in whom thromboembolism developed in relation to an acute event leading to hospitalization and who to the best of our knowledge had no chronic disease prior to this event. The controls would be women experiencing similar acute events who did not have a thromboembolic complication, matched on demographic factors and also, within broad categories, on the severity of the acute event.

Material and Methods

This investigation began about midway through the larger study.[4] From this point on, cases were actively collected in the study hospitals and abstracts of the medical records already on file were searched for additional cases. A case consisted of any woman 15-44 years of age who met the criteria for the main study except that her thromboembolic disease developed subsequent to surgery, trauma, systemic infection, or a period of immobilization. Their controls were selected in the field concurrently with cases identified in the hospitals. For the cases retrieved from the files, matched controls were found among those who had been previously chosen as controls for idiopathic cases but had not been used, since in the main study two potential controls were selected for each case and the second was used only when the first was unavailable. Controls met the same criteria as cases except that they did not develop thromboembolism. They were individually matched to the cases on race, marital status (married, not married), age within ten years, and date of discharge within one year. Matching was also done within three broad categories depending on the severity of the inciting event. These categories were somewhat arbitrarily established in the effort to distinguish different degrees of predisposition to thromboembolism—possibly predisposing, probably predisposing, and strongly predisposing. (Table 1) Where possible, two controls were selected per case to avoid problems of nonresponse. There were 113 cases and 184 controls thus selected.

It would have been desirable to interview the cases and controls as was done in the main study, but the timetable and limited funds made this impracticable. Instead, a

Table 1—Distribution of Cases and Controls by Diagnostic Categories of the Inciting Event

	Cases	Controls
Possibly predisposing		
Superficial trauma	15	0
Facial or extremity surgery (without immobilization)	5	17
Mild or moderate skin and systemic infections	10	9
Immobilization alone (long car ride, etc.)	3	0
Lumbosacral strain	0	1
	33	27
Probably predisposing		
Fractures	6	5
Extremity surgery with immobilization	3	1
Abdominal surgery	11	23
Severe systemic infection	1	0
	21	29
Strongly predisposing		
Extensive superficial trauma	0	2
Trauma to back with immobilization	1	1
Back surgery with immobilization	4	1
Abdominal surgery with complications	1	0
	6	4

shortened version of the interview was developed for use as a questionnaire to be mailed to the respondent, filled out by her, and returned by mail. This questionnaire contained questions on general health, medications frequently used (e.g., analgesics, tranquilizers, thyroid), methods of weight control employed, weight at time of hospitalization, and reproductive history. Questions on marital status, income, and education at the time of hospitalization were also asked. The questions on oral contraceptives included a list of all products known to be on the market during the period of the study and a calendar to be filled in if any of these had been taken within two years prior to hospitalization. Of the women responding, only two apparently did not understand how to fill in the calendar. Where necessary, permission was obtained from the patient's physician prior to mailing the questionnaire. The initial mailing contained the questionnaire and a covering letter along with a stamped return envelope. A similar mailing was sent if no response was received within a month. In case there was no response to this, a third and final questionnaire was dispatched by registered mail. Of the 179 total responses. 96 (54%) were to the first mailing, 66 (37%) were to the second, and registered letters accounted for 17 (9%). Of the 118 non-responses, 46 (39%) were because the available address was inadequate and the letters were returned undelivered. The remaining 72 (61%) apparently received the questionnaires but did not return them.

Nine of 18 Negro women with thromboembolism responded, as did 10 of 28 potential Negro controls. It seemed wisest to omit all these women from the analysis because of the low response rate and small numbers. It may be noted that they included seven case-control pairs, among whom two cases and one control had been taking oral contraceptives within one month of admission to the hospital.

Results

The remaining analysis is based on the 60 Caucasian pairs assembled from the responses to the mailed questionnaire. Completed forms were received from 62 of the 95 Caucasian cases (65%) and 98 of 156 Caucasian controls (63%). These respondents were compared with those who did not answer or could not be contacted. (Table 2) The non-respondent cases and controls did not differ significantly from the respondents by marital status, age, year of discharge, or religion. There was a larger percentage (57) of non-married cases among the non-respondents than among respondents (39), but this difference did not attain significance.

Two of the cases were rejected, one because of a history of previous thromboembolism revealed on the questionnaire, and the other because of failure to fill in the information on oral contraceptives correctly. Two controls were also rejected because of information in the responses. Fifty of the 60 cases had had thrombophlebitis of the lower extremities subsequent to the inciting event, three had had thrombophlebitis and a pulmonary embolus, and another three had had a pulmonary embolus alone. One case had had thrombophlebitis and a cerebrovascular accident, another a myocardial infarction, another a popliteal artery thrombosis, and one an axillary vein thrombosis. These cases did not all have paired controls who had answered, and for some the control was not as good a match as was possible considering other controls who had responded. Prior to knowledge of contraceptive use, those cases not matched adequately were re-matched from the pool of controls so that all cases were paired. In 46 instances both members of the pair were from the same city, and in 14 the case and control resided in different cities. These 14 pairs were not demographically different from the others. In the main study, no significant difference in oral contraceptive use was found between these cities, and there seemed to be no bias in pairing them.

Table 3 shows the distribution of cases and controls by the attributes for which they were matched. They were also similar in characteristics ascertained from the questionnaire. (Table 4) Cases were similar to controls in education and religion. The number of Catholics in the study and in the sample as a whole was unexpectedly high; there is no obvious explanation for this occurrence. The cases were also like the controls with respect to number of children and family income. The non-married women were not included in the comparisons as to number of children or as to their income, because there was confusion as to whether they were reporting their family's or their personal income.

The case-control comparison on weight showed some disparity. Where possible, the weight stated on the hospital chart was used, but for almost half the cases and controls the woman's statement on the questionnaire was the only figure available. Overall, the cases were heavier than the controls, but this difference was not statistically significant. The non-married cases and controls were nearly identical in weight, averaging 132 pounds; thus the overall

Table 2—Comparison of Caucasian Respondents and Non-respondents with Regard to Marital Status, Age, Year of Discharge, and Religious Affiliation

	Cases			Controls		
	Responding	Not responding	P[1]	Responding	Not responding	P[1]
Marital status at hospitalization						
Married	38	14		57	31	
Not married	24	19	0.2>P>0.1	41	27	>0.5
Age at hospitalization						
15-19	5	6		6	3	
20-24	17	6		17	13	
25-29	8	4		13	14	
30-34	13	6		7	14	
35-39	12	7		16	11	
40-44	5	4	>0.5	1	3	0.5>P>0.3
Year discharged						
1964	8	7		10	7	
1965	14	10		14	16	
1966	22	9		25	20	
1967	13	6		9	11	
1968	3	1	>0.5	2	4	>0.5
Religion						
Protestant	16	8		10	14	
Catholic	25	16		26	26	
Jewish	17	8		19	15	
Other	2	1	>0.5	5	3	>0.5

[1] P - The probability that a difference between respondents and non-respondents as large as, or larger than, the observed difference would occur by chance.

Table 3—Comparison of Cases and Controls with Regard to Characteristics on Which Matching was Attempted

	Cases	Controls
Degree of predisposition		
Possibly	33	27
Probably	21	29
Strongly	6	4
Marital status		
Married	37	37
Not married	23	23
Age		
15-19	5	6
20-24	17	17
25-29	8	13
30-34	13	7
35-39	12	16
40-44	5	1
Year of discharge		
1964	8	10
1965	14	14
1966	22	25
1967	13	9
1968	3	2

difference was due to the married subjects. The married cases averaged 143 pounds and the married controls 128 pounds. This difference, while considerable, was not statistically significant when the weights were grouped. If the difference was real and not due to selection bias, one would expect the weights of non-married subjects to be distributed in the same way. This would also be true if excess weight were a risk factor in the development of thromboembolic disease. The reason for this difference by marital status is not apparent. A similar number of cases and controls held jobs or were students at the time of their hospitalization. Eleven cases and nine controls had some connection with the medical profession.

Twenty-one cases and ten controls had taken oral contraceptives in the month prior to hospitalization, and most of these had discontinued use only on admission. The percentages of cases and controls using oral contraception in this study (35% and 16.7%, respectively) were quite similar to those in the main study (38.3% and 13.5%, respectively).

There were 13 pairs in which the case had been taking oral contraceptives in the month before admission and the control had not, and two pairs in which the reverse was true. (Table 5) The analysis appropriate for matched-pair studies[14] yields a relative risk of 6.5. The probability

Table 4—Comparison of Cases and Controls on Factors Other than Those for Which Matching was Done

	Cases	Controls		Cases	Controls
Religion			Weight (lbs.)		
Protestant	16	10	119 or less	8	17
Catholic	25	26	120-139	29	28
Jewish	17	19	140-159	13	10
Other	2	5	160+	10	5
0.5>P>0.3			0.2>P>0.1		
Education - grade completed			Weight of married subjects		
8 or less	5	1	119 or less	4	11
9-11	4	4	120-139	15	17
12	14	21	140-159	10	6
13-15	22	20	160+	8	3
16	6	8	0.1>P>0.05		
17+	9	6	Family income (limited to married subjects)*		
0.5>P>0.3			$6,000 or less	6	4
Number of children (limited to married subjects)			$7,000-8,999	9	7
0	7	4	$9,000-10,999	8	9
1	12	8	$11,000-15,999	11	6
2	8	12	$16,000 or more	3	8
3	6	7	0.5>P>0.3		
4+	4	6			
P>0.5					

* Three controls did not indicate their family income.

Table 5—Comparison of 60 Cases and 60 Matched Controls According to Use of Oral Contraceptives Within the Month Prior to Admission

		Matched Pairs Controls			
		Used	Not used	Total	
Cases	Used	8	13	21	R=13/2=6.5
	Not Used	2	37	39	P=.0074
		10	50		

Table 6—Comparison for All Respondent Cases and Controls According to Use of Oral Contraceptives Within the Month Prior to Admission (Non-matched Comparison)

	Used	Not used	Total	
Cases	21	39	60	R = 2.7
Controls	16	80	96	.02>P>.01
	37	119	156	

that a difference as extreme as this will occur by chance is 0.007, taking into account only the discrepant pairs.

The risk estimate yielded by a matched-pair analysis, as shown in Table 5, is much higher than that yielded by the method that would have been appropriate if the cases and controls had not been individually matched. The latter method gives a relative risk of 2.7.

The 36 potential controls who returned the questionnaire but were not paired with cases may also be taken into consideration if a matched-pair analysis is not used. Table 6 shows that the relative risk when the 60 cases are compared with the 96 total controls is again 2.7, with X^2 value of 5.9. In other words, inclusion of all the 96 controls who were available, of whom 36 had not been matched to cases, produces no change in the degree of association of thromboembolism with oral contraception. This tends to support the belief that, in selecting controls to be matched to cases, no bias was introduced.

Four cases and the same number of controls had used oral contraceptives at one time but had discontinued using them before the month immediately preceding admission. This finding is in agreement with the main study in showing that the increased risk terminates soon after ingestion of oral contraceptives is discontinued. There was no difference in duration of use between the 21 cases and 10 controls who were taking oral contraceptives within one month of admission: 33% of the cases and 30% of the controls had been taking this medication for longer than two years. This finding, too, was consistent with the main study.

The patients in this study did not have the opportunity to see samples of the various oral contraceptives, as did those in the main study, and a much larger proportion of those who returned the questionnaire indicated that they could not recall the name of the product they had used. Furthermore, the intervals from hospitalization to query were longer for these patients than for those in the main study. Of 31 patients who had been using an oral contraceptive within a month before admission to the hospital, eight

Table 7—Use of Combined Oral Contraceptives Within the Month Prior to Admission, by Type of Product, for Interviewed Subjects and Subjects in This Study

Estrogen	Progestin	Interviewed subjects		This study		Combined series	
		Cases	Controls	Cases	Controls	Cases	Controls
Mestranol .075 mg or more	Norethynodrel 2.5 mg or more	16	2	6	0	22	2
Mestranol Less than .075 mg	Norethynodrel 2.5 mg or more	5	2	2	0	7	2
Mestranol	Norethindrone	19	12	0	2	19	14
Mestranol	Ethynodiol	4	3	1	1	5	4
Ethinyl estradiol	Norethindrone	3	4	3	1	6	5
Ethinyl estradiol	Medroxyprogesterone acetate	1	0	2	1	3	1
Total		48	23	14	5	62	28

Table 8—Use of Oral Contraceptives by Cases and Controls by Religion, Weight (Married), and Response to Mailing

	Cases			Controls		
	Number	Using OC's	%	Number	Using OC's	%
Religion						
Protestant	16	6	37.5	10	1	10.0
Catholic	25	9	36.0	26	5	19.4
Jewish	17	4	23.5	19	3	15.8
Other	2	2	100.0	5	1	20.0
Weight (married)						
119 or less	4	2	50.0	11	5	45.4
120 - 139	15	7	46.5	17	3	17.7
140 - 159	10	6	60.0	6	1	16.7
160+	8	2	25.0	3	0	0
Responded to mailing number						
1	26	9	34.6	36	5	13.9
2	25	9	36.0	18	4	22.2
3	9	3	33.3	6	1	16.6

identified a product but could not name the strength. This makes the information on product less reliable for these persons. However, the findings are generally consistent with those obtained by interview in the main study. They are presented in Table 7, where it is shown that the highest ratio of case-users to control-users (22:2) for both studies for the combined form of oral contraceptives was the combination of mestranol in dosage of 0.075 mg or more with norethynodrel in dosage of 2.5 mg or more. Since norethynodrel has estrogenic activity,[15] the high ratio for this product may be the result of its high estrogen effect, as suggested by Inman and others.[16] In the present study, only one women (a case) had been using a sequential product, bringing the combined total to 16 case-users of sequentials and no control-users.

Discussion

Several interesting aspects of this study were analyzed further. The use of oral contraceptives was tabulated by religion, weight (of married cases), and letter to which the case or control responded. (Table 8) There was no striking difference in oral contraceptive use by religion. In this study Catholic women reported using oral contraceptives at the same rate as women of other faiths, tending to rule out under-reporting by this group. Use of oral contraceptives was in the main limited to married cases and controls. The distribution of their use by weight might suggest that excess weight has confounded the increased risk due to oral contraceptive use, or that weight acted independently as a risk factor (especially over 160 pounds).

However, the numbers are small, and the relationship between weight and oral contraceptives as risk factors is not clear. There was no difference in the use of oral contraceptives related to the mailing to which a case or control responded; that is, users did not hold back in responding to the questionnaire only to be finally encouraged by a registered letter.

This and the previous similar study in Great Britain[1,3] have demonstrated an increased risk of thromboembolic disease for women using oral contraceptives who are already in high-risk situations. Similar findings hold for postpartum women given estrogen to suppress lactation.[5,6] Thus the increased risk due to use of this medication is not limited to healthy women at what might be considered baseline risk. Perhaps this relationship will be shown to apply to women with chronic diseases as well. The authors of the British study raised the question of discontinuation of oral contraceptives one month prior to elective surgery and pointed out that each patient's physician must weigh the risk of postoperative thromboembolism against the risk of pregnancy; we can only concur.

Summary

Hospitalized female patients aged 15-44 who developed venous thrombosis or pulmonary embolism after sustaining trauma or surgery were studied with matched controls. The subject cases were collected in a previously reported investigation of idiopathic thromboembolism and were ineligible for that study. Information on prior use of oral contraceptives and other matters was secured by means of a questionnaire sent through the mails. Sixty cases and 97 controls responded; 21 cases (35%) and 16 controls (16%) had been using an oral contraceptive within the month prior to hospitalization. For 60 matched case-control pairs the relative risk for oral contraceptive users was estimated at over sixfold.

The findings support those of previous studies which indicate a relationship between both idiopathic and trauma-precipitated thromboembolism and the use of oral contraceptives.

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References

1. Royal College of General Practitioners. Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Practit. 13:267-79, 1967.
2. Inman, W. H. W. and Vessey, M. P. Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. Brit. Med. J. 2:193-99, 1968.
3. Vessey, M. P. and Doll, R. Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J. 2:651-57, 1969.
4. Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R.; and Smith, H. D. Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study. Am. J. Epid. 90,5:365-80, 1969.
5. Daniel, D. G.; Campbell, H.; and Turnbull, A. C. Puerperal Thromboembolism and Suppression of Lactation. Lancet, 287-89 (Aug., 1967).
6. Tindall, V. R. Factors Influencing Puerperal Thromboembolism. J. Obstet. Gynaec. Brit. Cwlth. 75:1324-27, 1968.
7. Veterans Administration Cooperative Urological Research Group: Treatment and Survival of Patients with Cancer of the Prostate. Surg. Gynec. Obstet. 124:1011-17, 1967.
8. Bailar, J. C., III and Byar, D. P. (Veterans Administration Cooperative Urological Research Group): Estrogen Treatment for Cancer of the Prostate: Early Results with Three Doses of Diethylstilbesterol and Placebo. Cancer 26:257-61, 1970.
9. Coronary Drug Project Research Group: The Coronary Drug Project: Initial Findings Leading to Modifications of its Research Protocol. J.A.M.A. 214, 7:1303-13, 1970.
10. Vessey, M. P. and Weatherall, J. A. C. Venous Thromboembolic Disease and the Use of Oral Contraceptives. A Review of Mortality Statistics in England and Wales. Lancet 2:94-6 (July, 1968).
11. Sartwell, P. E. and Anello, C. Trends in Mortality from Thromboembolic Disorders. In Second Report on The Oral Contraceptives by the Food and Drug Administration Advisory Committee on Obstetrics and Gynecology, August 1, 1969.
12. Markush, R. D. and Turner, S. L. Epidemiology of Exogenous Estrogens. HSMHA Health Reports, 86:74-86, 1971.
13. Vessey, M. P.; Doll, R.; Fairbairn, A. S.; and Glober, G. Postoperative Thromboembolism and the Use of Oral Contraceptives. Brit. Med. J. 3:123-26, 1970.
14. Pike, M. C. and Morrow, R. H. Statistical Analysis of Patient-Control Studies in Epidemiology. Factor under Investigation an All-or None Variable. Brit. J. Prev. Soc. Med. 24:42-4, 1970.
15. Drill, V. A. Oral Contraceptives. New York: McGraw-Hill, 1966, pp. 20-21.
16. Inman, W. H. W.; Vessey, M. P.; Westerholm, B.; and Engelund, A. Thromboembolic disease and the steroidal content of oral contraceptives: a report to the committee on safety of drugs. Brit. Med. J. 2:203, 1970.

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