

## PAPERS AND ORIGINALS

## Recurrence of Venous Thromboembolic Disease and Use of Oral Contraceptives

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### Summary

In 1969 this department reported on 42 women who had developed "idiopathic" venous thromboembolism while using oral contraceptives and 42 women who had developed the disease in the absence of such exposure. We have traced the subsequent history of these women to obtain information about recurrence of the disease.

During the follow-up period the risk of recurrence of thromboembolism during pregnancy or the puerperium appeared to be much the same irrespective of whether or not oral contraceptives had been in use at the time of the index attack. Recurrences unassociated with childbearing however, occurred about four times more often among women who had not been using oral contraceptives at the time of the index attack than among women who had been doing so. None of these findings was influenced by the use of oral contraceptives during the follow-up period, since exposure to the preparations was negligible after the index attack.

### Introduction

In 1969 Vessey and Doll reported the results of a retrospective study of the relation between oral contraceptives and thromboembolic disease. The patients investigated included 84 married women aged 16 to 40 years who had been admitted to hospital during the years 1964-7 for treatment of deep vein thrombosis or pulmonary embolism without evident predisposing cause. Of these 84 women 42 had been using oral contraceptives within

the month preceding the onset of their illness while 42 had not.

It occurred to us that women developing thromboembolism while using oral contraceptives (and subsequently discontinuing them) might be at less risk of recurrence of the disease than women developing thromboembolism in the absence of exposure to oral contraceptives. To test this hypothesis we decided to trace the history of the women included in the study of Vessey and Doll to the end of 1972.

### Patients and Methods

A letter was sent to each woman's general practitioner requesting permission to contact her. Whenever this was obtained a questionnaire was sent to the woman to inquire about her obstetric and menstrual history, her use of oral contraceptives, and any recurrence of thromboembolism after the index hospital admission. If the woman did not return the questionnaire an attempt was made to contact her by telephone or to interview her at home. Five general practitioners withheld permission to contact their patients; of these, four succeeded in obtaining the information requested themselves.

Each woman who reported a recurrence was asked to state the date when it occurred, the name of any hospital at which she received treatment, details of management and outcome, and any illness or injury predisposing to the episode. No attempt was made to distinguish superficial from deep vein thrombosis and any reported event was accepted as a recurrence. As all the women in the study had suffered a previous thromboembolic episode it seemed reasonable to assume that their reporting of recurrences would be sufficiently accurate for our purposes.

In all, 76 completed questionnaires were obtained, and it was established that one patient had died from a cerebral tumour and that two had emigrated. No information was obtained for five patients; of these, three had been using oral contraceptives at the time of the index hospital admission and two had not.

In the original study by Vessey and Doll the patients were interviewed in their homes or were sent postal questionnaires some time after the index hospital admission (mean interval 20 months). The available follow-up data from the original study have therefore been used in the present analysis for the eight women about whom no additional information was obtained.

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## Results

### COMPARABILITY OF GROUPS

At the time of the index hospital admission the two groups were closely comparable with respect to age, parity, and diagnosis. There were, however, slightly fewer women with a past history of thromboembolism among those who were using oral contraceptives than among those who were not (table I). This difference did not approach statistical significance ( $P=0.30$ ).

TABLE I—Comparison of the Two Groups of Women at Time of Index Hospital Admission

	No. of Women	
	On oral Contraceptives (n = 42)	Not on Oral Contraceptives (n = 42)
Age (years):		
≤20	0	2
21-30	20	19
31-40	22	21
Parity (number of stillbirths or live births):		
0	8	7
1-2	19	24
≥3	15	11
Past history of thromboembolism:		
Positive	12	17
Negative	30	25
Discharge diagnosis:		
Deep vein thrombosis	20	23
Pulmonary embolism	10	6
Deep vein thrombosis and pulmonary embolism	12	13

Of the 76 women for whom completed questionnaires were obtained only three had used oral contraceptives at any time after the index hospital admission, two in the group of former oral contraceptive users (for a total of 20 woman-months) and one in the group without such exposure (for a total of 24 woman-months). In addition, of the eight women for whom only partial follow-up data were available, one (a non-user of oral contraceptives at the time of the index hospital admission) had been taking oral contraceptives for 11 days at the time of her interview. Three of these four women who subsequently used oral contraceptives did not report any recurrence of thromboembolism; the fourth suffered a recurrence six years *before* she began to use oral contraceptives. From these data it is clear that the use of oral contraceptives subsequent to the index hospital admission cannot have influenced the results.

### RECURRENCE OF THROMBOEMBOLISM IN ASSOCIATION WITH PREGNANCY AND THE PUERPERIUM

The childbearing experience of the women in the two groups during the follow-up period was almost identical (table II). Three women in each group reported a recurrence of thromboembolism occurring during pregnancy or the puerperium. In each instance the woman was already in hospital when the recurrence was diagnosed. No woman reported more than one such recurrence.

TABLE II—Childbearing Experience of the Two Groups of Women during Follow-up Period

	On Oral Contraceptives at time of Index Admission	Not on Oral Contraceptives at time of Index Admission
Number of women becoming pregnant	15	15
Number of pregnancies	24	24
Outcome of pregnancies:		
Livebirth	12	16
Stillbirth	0	0
Miscarriage	8	6
Termination	4	2

### RECURRENCE OF THROMBOEMBOLISM AT TIMES OTHER THAN DURING PREGNANCY AND THE PUERPERIUM

Analyses of the recurrence of thromboembolism unassociated with childbearing in the two groups were made by life table methods. Each woman entering a particular analysis remained in the "at-risk" group until she suffered her first recurrence, was lost to follow-up, or reached the study closure date. A woman also left the "at-risk" group when she became pregnant and re-entered it three months after delivery, miscarriage, or termination of pregnancy. No recurrences associated with pregnancy or the puerperium were included in the life table or significance test calculations.

Altogether five of the women who had been using oral contraceptives at the time of the index hospital admission reported recurrences during the follow-up period, in comparison with 19 of those who had not been using them. The proportions of women remaining free from recurrence of thromboembolism in the two groups in relation to the time elapsed since the index hospital admission are shown in fig. 1. After three years 92% of the women in the group of former oral contraceptive users were free from recurrence in comparison with 64% of those in the group without such exposure. After six years 86% of the former oral contraceptive users and 57% of the non-users were free from recurrence. The overall difference in the recurrence rate between the two groups is statistically significant ( $P < 0.01$ ) when analysed by the logrank method (Peto and Pike, 1973).

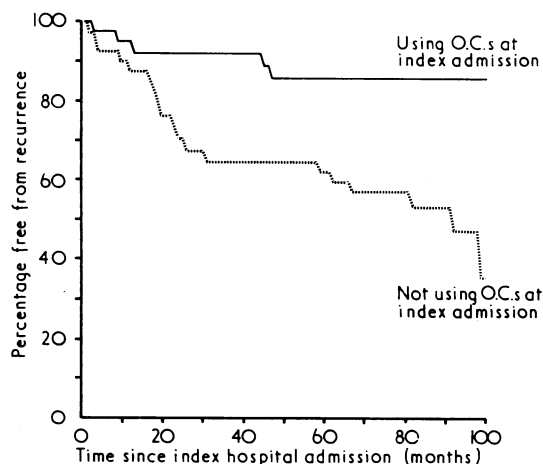


FIG. 1—Percentages of patients free from recurrence of thromboembolism in relation to time since index hospital admission. O.C. = Oral Contraceptive.

An analysis of the data concerning only those recurrences necessitating hospital admission is shown in fig. 2. Three of the women who had been using oral contraceptives reported such a recurrence in comparison with 12 of the women who had not been using oral contraceptives. Despite the small numbers the overall difference in the recurrence rate between the two groups remains statistically significant ( $P < 0.05$ ).

Because the proportions of women giving a past history of thromboembolism at the time of the index hospital admission were slightly different in the two groups (table I) separate analyses were undertaken for women with and without such a history. The life tables are not shown here but it may be noted that the more favourable experience of the women who formerly used oral contraceptives cannot be explained in these terms. The numbers of women at risk and the numbers suffering recurrences in the different subgroups are shown in table III.

All the above analyses take only *first* recurrences of thromboembolism into account. Many women, however, reported multiple recurrences. Details are shown in table IV.

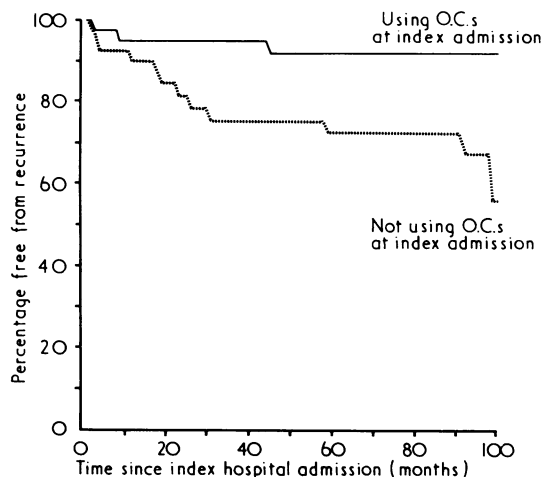


FIG. 2—Percentages of patients free from recurrence of thromboembolism needing hospital admission in relation to time since index hospital admission. O.C. = Oral Contraceptive.

TABLE III—Recurrence of Thromboembolism in the Two Groups of Women in relation to Past History at Time of Index Hospital Admission

	On Oral Contraceptives at Time of Index Admission	Not on Oral Contraceptives at Time of Index Admission
<b>No past history of thromboembolism:</b>		
Number of women	30	25
Number suffering recurrence	3	10
Number suffering recurrence requiring hospital admission	1	6
<b>Past history of thromboembolism:</b>		
Number of women	12	17
Number suffering recurrence	2	9
Number suffering recurrence requiring hospital admission	2	6

TABLE IV—Number of Women in the Two Groups reporting different Numbers of Recurrences

No. of Recurrences	On Oral Contraceptives at Time of Index Admission	Not on Oral Contraceptives at Time of Index Admission
<b>All recurrences:</b>		
1	2	11
2	0	3
3	1	2
≥4	2	3
<b>Recurrences requiring hospital admission:</b>		
1	1	6
2	0	2
3	1	2
≥4	1	2

**Discussion**

In the present study recurrences of thromboembolism were reported by the patients themselves, and before drawing any firm conclusions it is important to ask whether this method of collecting information is valid. Data provided by the women about the treatment they received strongly suggest that most reported recurrences were, in fact, diagnosed as episodes of venous thrombosis or pulmonary embolism. Of the 15 women who reported recurrences which were unassociated with pregnancy or the puerperium and which required hospital admission 12 remembered that they had been treated with anticoagulants; of the remaining three one stated that she had been treated with a “saline drip” and another described treatment by femoral vein ligation. Of those women reporting recurrences that did not need hospital admission half said that they had been treated with anticoagulants while all but one of the remainder described other appropriate forms of treatment such as tight bandaging.

Even though it seems probable that the great majority of reported recurrences were valid there is no assurance that every woman recalled all her recurrences. As a partial check on the completeness of reporting, the questionnaires of the woman who had described a recurrence in the original follow-up period were examined. Only one of the 12 such women failed to report the recurrence again; she had suffered the recurrence in 1964, only four months after her index hospital admission. Furthermore, of the 11 women who again reported recurrences 10 gave the same diagnosis, date, and treatment details as they had given shortly after the disease had recurred; the remaining woman, though reporting a recurrence, gave a different date. These data suggest that reporting of further episodes of thromboembolism may have been reasonably complete; in any case there does not seem to be any reason to suspect bias in recall between the two groups.

As a result of these considerations we conclude that women who develop venous thromboembolism while using oral contraceptives, and subsequently discontinue them, have a smaller risk of suffering a recurrence than women developing the disease in the absence of exposure to oral contraceptives. This situation does not seem to apply during pregnancy or the puerperium, though the data in the present study are too few to draw a firm conclusion on this point.

We thank Miss Keena Jones for help in tracing and interviewing the patients.

**References**

Peto, R., and Pike, M. C. (1973). *Biometrics*. In press.  
 Vessey, M. P., and Doll, R. (1969). *British Medical Journal*, 2, 651.