Papers and Originals

Postoperative Thromboembolism and the Use of Oral Contraceptives

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Summary: We have previously reported the results of a retrospective study of the relationship between oral contraceptives and deep vein thrombosis and pulmonary embolism occurring in the absence of an evident predisposing cause. The present paper describes a similar investigation of the relationship between oral contraceptives and thromboembolism following certain surgical procedures.

Of 30 patients with thromboembolism, 12 (40%) had been using oral contraceptives during the month preceding surgery, while only 9 of 60 matched controls (15%) had been doing so. From these data it is estimated that the risk of postoperative thromboembolism is increased threefold to fourfold by the use of contraceptive steroids.

It is recognized that few of the episodes of deep vein thrombosis and pulmonary embolism that occur post-operatively are detectable clinically, and that not all of these are recorded in discharge summaries or diagnostic indexes. Despite these considerations, we have been unable to detect any important bias in the data which could account for the observed association between oral contraceptives and the development of postoperative thromboembolism.

Introduction

A causal relationship between the use of oral contraceptives and deep vein thrombosis and pulmonary embolism occurring in previously healthy women has now been established by four controlled retrospective studies (Royal College of General Practitioners, 1967; Inman and Vessey, 1968; Vessey and Doll, 1968, 1969; Sartwell *et al.*, 1969). No such investigations have yet been reported, however, concerning the risks of oral contraception in women with conditions known to predispose to thromboembolic disease, such as a recent surgical operation, the collagen disorders, or rheumatic heart disease. We describe here the results of a retrospective study, carried out in the North-West Metropolitan and Oxford hospital regions, of the relationship between the use of oral contraceptives and venous thromboembolism following certain surgical procedures.

Methods

North-West Metropolitan Region

Diagnostic indexes were searched at the 19 large general hospitals that had participated in our earlier investigations (Vessey and Doll, 1968, 1969) to identify married women

aged 16-40 years recorded as having suffered venous thrombosis or pulmonary embolism within one month of a surgical operation (other than an obstetrical procedure) during 1964-7. These patients were then divided into two groups: (a) those who had undergone an operation which would have been accepted as appropriate (in the absence of thromboembolism) for control purposes in our earlier investigations, and (b) those who had not. This categorization was made before the case records were examined and in the absence of any knowledge concerning the patients' methods of contraception.

The hospital notes relating to patients who had an acceptable operation were then reviewed to identify subjects who were not eligible for inclusion in the study according to the criteria defined in our earlier work—that is, those who had a relevant chronic disease, were pregnant or had been pregnant within the three months preceding the operation, were post-menopausal or sterilized, had suffered only superficial thrombophlebitis, or could not be interviewed because they had died during their stay in hospital. The remaining patients were then interviewed in their homes, using our original questionnaire, by the same medical social worker (Miss Keena Jones) who had interviewed patients in our earlier studies. As before, a few patients who could not be interviewed answered our questions by post.

For each affected patient two controls were selected from among the 168 included in our original investigations such that matching was achieved for age (within five years), parity (within groups 0, 1-2, or 3 or more deliveries), and year of admission. Matching with respect to hospital was not attempted.

Oxford Region

The procedure for identifying patients with postoperative thromboembolism in the Oxford region was essentially the same as that used in the North-West Metropolitan region, save that the files of the Oxford Record Linkage Study (Acheson, 1968) were used as the original source of information. These files covered a population of about 340,000 in 1964-5 and were extended to cover a population of about 780,000 in 1966-7. The method of classifying and assessing the case records was exactly as described for the North-West Metropolitan region.

Two controls who had undergone similar surgical procedures, but had not developed thromboembolism, were selected to match each of the eligible patients with postoperative deep vein thrombosis or pulmonary embolism. In addition to matching for age, parity, year of admission, and absence of any of the attributes used to exclude affected patients, the controls were also selected from hospitals in the same area as the one to which the corresponding patient with thromboembolism had been admitted.

The affected patients and their matched controls were interviewed in their homes by Miss Keena Jones, save for a small number who answered a postal questionnaire instead.

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Material

Of the 129 patients identified as having suffered postoperative thromboembolism 82 were in the North-West Metropolitan region and 47 in the Oxford region (Table I). Of these, 60 and 32 respectively had undergone a surgical procedure which would not have been accepted as appropriate for control purposes in our earlier investigations, as the presence of the condition for which the operation was performed might have influenced the woman's contraceptive habits. Of the remaining 22 patients in the North-West Metropolitan region one had died in hospital from massive pulmonary embolism after excision of a haemangioendothelioma, and one who developed deep vein thrombosis after a skin biopsy was excluded from the study because she had been in hospital for several weeks with sarcoidosis before this occurred. The remaining 20 patients were interviewed (18) or completed a postal questionnaire (2).

TABLE I.—Surgical Procedures Undergone by Patients Developing Postoperative Venous Thrombosis or Pulmonary Embolism in North-West Metropolitan and Oxford Regions

Operation	North-West Metropolitan Region	Oxford Region
Operations not acceptable for control purposes by Vessey and Doll (1968, 1969):		
Gynaecological operations	49	26
Varicose vein operations	5	3
Gastrectomy, colectomy	2	2
Other operations	4	1
Total ..	60	32
Operations acceptable for control purposes by Vessey and Doll (1968, 1969):		
Appendectomy	4	7
Orthopaedic procedures	5	2
Operations for ureteric or renal calculi ..	3	3
Herniorrhaphy	3	1
Cholecystectomy	3	0
Excision of lipoma, ganglion, etc. ..	2	0
Other operations	2	2
Total ..	22	15

Fifteen patients in the Oxford region developed thromboembolism after an acceptable operation. Of these, two were excluded from the study because they had suffered only superficial thrombophlebitis (one after haemorrhoidectomy and one after exploration of a stab wound), and one because she had been sterilized (this patient had developed deep vein thrombosis after nephrectomy for pyonephrosis complicating a ureteric calculus). In addition one patient, who had developed deep vein thrombosis after appendectomy, died in hospital from septicaemia. Of the remaining 11 patients nine were interviewed, one completed a postal questionnaire, and one could not be interviewed as she had gone abroad.

Twenty control patients were selected to match the 10 affected patients from whom information was successfully obtained, and all were either interviewed (16) or answered our questions by post (4).

In this way, data for 30 triads of patients, each consisting of one patient with postoperative thromboembolism and two matched controls, were obtained for analysis.

Results**Use of Oral Contraceptives**

Table II shows the proportion of patients in the North-West Metropolitan and Oxford regions who had been using oral contraceptives during the month before admission to hospital for surgery (or in the case of six control patients in the North-West Metropolitan region for the treatment of an

TABLE II.—Patients with Postoperative Thromboembolism and Matched Control Patients Classified by Use of Oral Contraceptives During Month Before Admission to Hospital (Percentages shown in Parentheses)

Region	Diagnostic Group	No. of Patients	
		Oral Contraceptives	
		Used	Not Used
North-West* Metropolitan.	Thromboembolism	7 (35)	13 (65)
	Control	4 (10)	36 (90)
Oxford†	Thromboembolism	5 (50)	5 (50)
	Control	5 (25)	15 (75)
Both regions‡	Thromboembolism	12 (40)	18 (60)
	Control	9 (15)	51 (85)

Pike's test for matched controls (Pike and Morrow, 1970).

* $\chi^2=4.1$, $n=1$, $0.05>P>0.01$. † $\chi^2=1.2$, $n=1$, $0.30>P>0.20$. ‡ $\chi^2=6.6$, $n=1$, $P=0.01$.

acute medical disease). In both regions the proportion who had been using oral contraceptives was higher among those who suffered postoperative thromboembolism than among the controls (North-West Metropolitan region 35% against 10%; Oxford region 50% against 25%)*. This difference was statistically significant in the North-West Metropolitan region ($P<0.05$) and in the two regions combined ($P=0.01$), but not in the Oxford region alone. The difference in the overall frequency of use of oral contraceptives between patients in the two regions was found to be largely attributable to differences in age, parity, and year of hospital admission; in this context it will be recalled that the Oxford Record Linkage Study covered a much larger population in 1966-7 than in 1964-5 (see methods).

A comparison was also made between the 30 patients with postoperative thromboembolism and all 188 control subjects included in the present and previous studies (Vessey and Doll, 1968, 1969). Allowance was made for age, parity, and year of admission to hospital, and the method of analysis described by Mantel and Haenszel (1959) was used. A statistically significant difference in the frequency of use of oral contraceptives was found ($\chi^2=7.7$, $n=1$, $0.01>P>0.001$).

The data were too few for detailed analysis of the types of oral contraceptive used or the duration of their use. It may be noted, however, that of the 10 patients with thromboembolism and seven controls who were able to provide the necessary information, seven and two respectively had been using oral contraceptives containing more than 50 μg . of oestrogen, and that the mean duration of use of the preparations was 22 months for the patients with thromboembolism and 16 months for the controls. These results are consistent with earlier findings that oral contraceptives containing higher doses of oestrogen are more hazardous (Inman *et al.*, 1970) and that the risk is unrelated to the duration of their use (Vessey and Doll, 1968, 1969; Sartwell *et al.*, 1969).

Comparability of the Groups

Comparisons were made between the patients with thromboembolism and their matched controls to see if any other factor could be identified which might account for the difference in their use of oral contraceptives. Age, parity, marital status, and year of admission had been taken into account during matching, and the groups were also found to be comparable with respect to country of origin, religion, social class, interval since the birth of the last child, and (in those without a history of previous thromboembolism) the

*Of the two patients who died, and who are not therefore included in Table II, one had definitely been using oral contraceptives and one had almost certainly not. The patient who had gone abroad had probably not been using the preparations.

presence of varicose veins. Special attention was paid to three other factors which had proved of special interest in our earlier work—the frequency of previous thromboembolic disease, the prevalence of cigarette smoking, and the distribution of obesity.

As in our previous studies, a higher proportion of the affected patients (5 out of 30) than of the controls (3 out of 60) reported a previous episode of thromboembolism. Among those with no such history, 10 out of 25 patients with thromboembolism and 9 out of 57 controls had been using oral contraceptives. There was little difference between the groups in smoking habits, the mean number of cigarettes smoked per day being four for the affected patients and five for the controls. The patients with thromboembolism were 4 lb. (1.8 kg.) heavier than the controls after adjustment had been made for age and height by means of the standard tables provided by Kemsley *et al.* (1962). This is consistent with the belief that obesity is a factor in the development of thromboembolism, but provides no explanation for the association between the use of oral contraceptives and the development of the disease, since obese women did not use oral contraceptives more frequently than non-obese women either in this study or in our earlier ones (Vessey and Doll, 1968, 1969).

Bias in Diagnosis and Recording

Recent work, in which the radioactive fibrinogen test and venography were used, has shown that few of the episodes of deep vein thrombosis that occur postoperatively are detectable clinically (Flanc *et al.*, 1968; Lambie *et al.*, 1970), and the same is undoubtedly true of pulmonary embolism. Furthermore, only a proportion of the episodes diagnosed clinically are recorded in discharge summaries or diagnostic indexes. In this context it is of interest to note that no fewer than 17 of the 30 affected patients in the present study were readmitted to hospital for treatment of thromboembolism, having previously been discharged after an apparently routine postoperative course. This is not surprising, as episodes of disease severe enough to require readmission to hospital would be more likely to be recorded than those merely occurring during the course of the normal postoperative stay.

It might be expected that recording of thromboembolism would be more complete in the Oxford region, because of the Oxford Record Linkage Study, than in the North-West Metropolitan region, and this, in fact, appears to have been so. In 1964-7, data concerning hospital admissions during approximately 450,000 woman years of observation in the age range 16-40 years were accumulated by the Oxford Record Linkage Study, while it may be estimated that a population three to four times as great was served by the 19 hospitals studied in the North-West Metropolitan region. It is shown in Table I, however, that rather fewer than twice as many episodes of postoperative thromboembolism were recorded in the latter region as in the former.

Despite these considerations, our present findings would be invalid only if thromboembolic disease were diagnosed more readily, or recorded more often, when patients had been using oral contraceptives than when they had not. That this could have occurred is indicated by the results of a postal inquiry which we made of 50 general surgeons working in the hospitals included in the present investigation. Ninety per cent. of them replied and nearly two-thirds stated that during the period 1964-7 they "routinely inquired about the use of oral contraceptives when a young woman under their care developed signs or symptoms suggestive of deep vein thrombosis or pulmonary embolism after an operation." It should be noted, however, that 17 of our 30 patients were readmitted to hospital with thromboembolism, having been previously discharged when apparently well. The decision to send patients back into hospital would usually have been made by the general practitioner rather than by the surgeon.

If diagnostic bias were the explanation for our results the association between the use of oral contraceptives and thromboembolism would, we believe, have been strongest in those for whom the physical basis for the diagnosis was least certain. As in our earlier investigations, we tested the hypothesis by asking a colleague (Dr. Patricia Fraser) to review abstracts of the case histories from which all reference to contraceptive practices had been omitted and to classify them according to the reliability of the diagnosis. The two patients who had died and the one who had gone abroad were included in this assessment, the results of which are shown in Table III.

TABLE III.—*Certainty of Diagnosis of Postoperative Thromboembolism According to Use of Oral Contraceptives by Affected Patients*

Certainty of Diagnosis	Deep Vein Thrombosis Only		Pulmonary Embolism Only		Deep Vein Thrombosis and Pulmonary Embolism		Total	
	Oral Contraceptives							
	Used	Not Used	Used	Not Used	Used	Not Used	Used	Not Used
Possible Probable Certain	1 3 1	5 5 0	0 5 0	3 3 0	— 0 3	— 0 4	1 8 4	8 8 4
Total	5	10	5	6	3	4	13	20

Among the 13 patients known to have been using oral contraceptives the diagnosis was graded as "probable" or "certain" in all but one, while among the 20 patients believed not to have been using the preparations this degree of confidence was placed in the diagnosis in only 12. The patients who were using oral contraceptives were not investigated more intensively than those who were not (Vessey, 1970), and these findings suggest that the observed association is unlikely to be due to a greater tendency to diagnose or record thromboembolic disease in women using oral contraceptives.

Size of Risk

From the data given in Table II, the risk of postoperative thromboembolism among women using oral contraceptives was calculated to be three to four times greater among women using oral contraceptives than among those not doing so (12/18 divided by 9/51 = 3.8 to 1).

An estimate of the relative risk was also obtained by comparing the 30 patients with thromboembolism with all 188 controls included in the present and previous studies, the method described by Mantel and Haenszel (1959) being used with allowance for age, parity, and year of admission to hospital. These computations provided an estimate identical to that obtained from the simple comparison already described—that is 3.8 to 1.

It is not possible to calculate the absolute risk attributable to oral contraceptives because of the incomplete ascertainment of episodes of postoperative thromboembolism, which has already been discussed. It is shown in Table I, however, that seven patients were recorded in the Oxford region as having suffered thromboembolism following appendicectomy, which is equivalent to an attack rate of about 12 per 1,000 patients undergoing the operation. If it is assumed that the use of oral contraceptives in the Oxford region during 1964-7 followed the national pattern and that the estimate of relative risk of 3.8 to 1 for users to non-users of oral contraceptives is correct, then the present data suggest that clinical thromboembolism following appendicectomy in the Oxford region occurs in at least 30 per 1,000 who use oral contraceptives and 8 per 1,000 not doing so.

Discussion

The present investigation suggests that the use of oral contraceptives before a surgical operation increases the subsequent risk of postoperative thromboembolism threefold to fourfold. The magnitude of the relative risk is thus estimated to be somewhat less than that previously found for thromboembolism occurring in the absence of predisposing factors (Vessey and Doll, 1968, 1969). It should be noted, however, that the number of patients in the present study was necessarily small and that the confidence limits of the estimate are wide.

This finding raises the question of whether or not patients should be advised to discontinue oral contraceptives for a while before undergoing elective surgical procedures. To find out about the existing practices in this respect, we included a special question in the postal inquiry that we made of the 50 general surgeons referred to previously. While only 10% of them stated that they advised young women to discontinue oral contraceptives for an interval before undergoing elective surgery during 1964-7, no fewer than half stated that this was their practice now. As always, however, the risks of oral contraception have to be balanced against the risks of unwanted pregnancy. These are not inconsiderable, and one surgeon commented, "I started to advise discontinuing oral contraceptives, but two patients promptly became pregnant. I have now reversed my decision. I fear the unwanted pregnancy more than the pill."

If oral contraceptives are to be stopped before elective surgery, for how long should they be stopped? The present investigation, and those that we made earlier, suggest that the increased risk of thromboembolism declines rapidly after discontinuation of medication, to become undetectable after four weeks. This finding is also in keeping with studies of the effects of oral contraceptives on blood clotting, in which it

has been shown that changes brought about by oral contraceptives return to normal within a few weeks of stopping (Dugdale and Masi, 1969).

We should like to express our thanks to Miss Keena Jones for tracing and interviewing the patients and to Dr. Patricia Fraser for assessing the case histories.

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REFERENCES

- Acheson, E. D. (editor) (1968). In *Record Linkage in Medicine*, p. 40. Edinburgh, Livingstone.
- Dugdale, M., and Masi, A. T. (1969). In *Second Report on the Oral Contraceptives by the Advisory Committee on Obstetrics and Gynecology*. Washington, D.C., U.S. Department of Health, Education and Welfare, Food & Drug Administration.
- Flanc, C., Kakkar, V. V., and Clarke, M. B. (1968). *British Journal of Surgery*, 55, 742.
- Inman, W. H. W., and Vessey, M. P. (1968). *British Medical Journal*, 2, 193.
- Inman, W. H. W., Vessey, M. P., Westerholm, B., and Englund, A. (1970). *British Medical Journal*, 2, 203.
- Kemsley, W. F. F., Billewicz, W. Z., and Thomson, A. M. (1962). *British Journal of Preventive and Social Medicine*, 16, 189.
- Lambie, J. M., *et al.* (1970). *British Medical Journal*, 2, 142.
- Mantel, N., and Haenszel, W. (1959). *Journal of the National Cancer Institute*, 22, 719.
- Pike, M. C., and Morrow, R. H. (1970). *British Journal of Preventive and Social Medicine*, 24, 42.
- Royal College of General Practitioners (1967). *Journal of the Royal College of General Practitioners*, 13, 267.
- Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. (1969). *American Journal of Epidemiology*, 90, 365.
- Vessey, M. P. (1970). M.D. Thesis. In preparation.
- Vessey, M. P., and Doll, R. (1968). *British Medical Journal*, 2, 199.
- Vessey, M. P., and Doll, R. (1969). *British Medical Journal*, 2, 651.

Relevance of Salt, Water, and Renin to Hypertension in Chronic Renal Failure

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Summary: Blood pressure control was examined in 75 patients with end-stage renal failure treated by regular twice-weekly haemodialysis. Dietary sodium was restricted and extracellular fluid was removed by ultrafiltration until blood pressure was normal or signs of salt depletion were observed. Failure of these measures constituted an indication for nephrectomy. Of the 75 patients, 18 were never hypertensive, 46 had hypertension which could be corrected by salt and water depletion, and 11 had persistent hypertension which could not be controlled in this way. Nine of these 11 patients underwent bilateral nephrectomy; in each of the seven in whom the post operative result could be evaluated the blood pressure returned rapidly to normal.

Plasma renin activity, measured in 34 subjects, was raised above normal in six out of nine patients whose

blood pressure could not be controlled by salt and water depletion and in one of the 11 patients whose blood pressure could be so controlled, but was within the normal range in all nine normotensive patients. The mean level of plasma renin activity in the first group was significantly higher than that of each of the other two groups.

There was a significant correlation between hypertension during dialysis and after transplantation, suggesting that, in addition to renin, there is a non-renal factor which predisposes certain patients to hypertension in the presence of salt and water excess.

Introduction

While it has been claimed that hypertension in patients with end-stage renal failure can always be controlled by adequate ultrafiltration during dialysis coupled with restriction of dietary sodium (Blumberg *et al.*, 1964; Comty *et al.*, 1964; McDonald, 1967) there are patients in whom blood pressure cannot be controlled by sodium depletion until both

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