Dr T R Terry, Dr Sheila Goldsworthy, and Miss Mary Bulbeck for their help.

The study was partly supported by the St George's Hospital Medical Research Fund.

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(*Accepted 26 July 1977*)

Oral contraceptive use and venous thromboembolism: absence of an effect of smoking

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British Medical Journal, 1977, **2**, 729-730

Summary

We conducted a case-control study to test the hypothesis that women smokers who use oral contraceptives have an increased risk of developing venous thrombosis. Patients and controls were drawn from two sets of hospital patients already included in the Boston Collaborative Drug Surveillance Programme. Sixty patients with uncomplicated thromboembolism were matched with 180 controls with other diagnoses; all were premenopausal women taking oral contraceptives. Patients with conditions that might predispose to thromboembolism or be related to smoking were excluded. We found no association between smoking habits and thromboembolism. Similarly, we found no association between thromboembolism, smoking, and duration of oral contraceptive use.

Thus we conclude that differences in fibrinolytic activity between smokers and non-smokers are not major factors in the aetiology of uncomplicated thromboembolism in women using oral contraceptives.

Introduction

Several studies have shown a substantial positive association between thromboembolic disease and the use of oral contraceptives.[1-4] This association may be explained by the enhanced concentrations of coagulation factors shown in the blood of women taking oral contraceptives.[5] A recent report suggests that this increase in concentrations of coagulation factors in oral contraceptive users is associated with a compensatory increase in fibrinolytic activity in non-smokers, but not in smokers.[6] This raises the possibility that smoking may predispose to thromboembolism in oral contraceptive users. We undertook a study to test this hypothesis, and report the results.

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Patients and methods

We obtained information from two independent sets of patients studied by the Boston Collaborative Drug Surveillance Programme. The first set (source 1) consisted of patients admitted consecutively to selected acute medical wards in hospitals in the USA. The second set (source 2) consisted of patients admitted consecutively to general medical and surgical wards of 24 hospitals in the greater Boston area in 1972. Patients were excluded from the second set if they had been admitted to hospital in the preceding three months, were too ill to interview, or were admitted for less than 72 hours, and so may have missed interview.

Patients were interviewed by trained nurses, who obtained information on demographic characteristics, personal habits (including smoking and alcohol consumption), and history of medication. Diagnoses at discharge were later obtained from the hospital records. Details of the exact methodology applied in the two studies have been given elsewhere.[1 7]

We confined our analyses to patients who were premenopausal oral contraceptive users. We further excluded patients with diabetes mellitus, obesity, acute myocardial infarction, lipid abnormalities, varicose veins, or pulmonary disease other than thromboembolic—all conditions which might predispose to the development of thromboembolism or be related to cigarette smoking. Also excluded were patients whose thromboembolism was secondary to trauma or surgical procedures. There remained for study a total of 63 patients admitted primarily because of uncomplicated deep venous thrombosis or pulmonary thromboembolism or both. For each such patient, three control patients were sought from the set of premenopausal oral contraceptive users. Patients and controls were matched for age (within a five-year tolerance), study source, and according to where they had been admitted to hospital. Sixty patients were successfully matched, although 14 of the resulting 180 controls were not matched for where they had been admitted to hospital simultaneously with the other factors. A detailed review of these 14 controls showed that their inclusion in the study did not affect the final results.

Among the 180 controls the primary diagnosis at discharge was gastrointestinal disease in 54 (30%), injury or orthopaedic conditions in 23 (13%), infection in 18 (10%), neurological disease in 14 (8%), genitourinary disease in 13 (7%), cardiovascular disease in 11 (6%), and haematological disorders in 9 (5%). Various other conditions were

TABLE I—*Relation between smoking habits and thromboembolism in oral contraceptive users*

	Patients with thromboembolism (n = 60)	Controls (n = 180)
Non-smokers*	26 (43%)	72 (40%)
<20 cigarettes/day	29 (48%)	86 (48%)
≥20 cigarettes/day	5 (8%)	22 (12%)

*Includes former smokers who had currently abstained for over one year.

TABLE II—*Effect of duration of oral contraceptive use on relation between thromboembolism and smoking habits*

Duration of oral contraceptive use (years)	Patients with thromboembolism		Total	Controls		Total*
	Smokers (%)	Non-smokers (%)		Smokers (%)	Non-smokers (%)	
<1	11 (46)	13 (54)	24	49 (54)	42 (46)	91
1–5	16 (59)	11 (41)	37	42 (66)	21 (33)	63
≥6	7 (78)	2 (22)	9	11 (61)	7 (39)	18

*Eight controls were excluded as duration of oral contraceptive use was not recorded.

reported in the remaining 38 (21%). The mean age of the 60 patients was 29 (±standard error of mean 1·0) years, and of the 180 controls was 26 (±0·5) years.

Results

Twenty-six (43%) of the oral contraceptive users with uncomplicated thromboembolism were non-smokers compared with 72 (40%) of the controls (table I). Likewise, five (8%) of the patients and 22 (12%) of the controls smoked more than 20 cigarettes daily. Thus there was no evidence of a relation between uncomplicated thromboembolism and smoking habits.

A review of the data in the light of information on duration of oral contraceptive use again failed to show an association between thromboembolism and smoking habits (table II). Furthermore, stratification of the patients according to where they had been admitted to hospital showed that this was not a confounding variable.

Discussion

This study provides strong evidence against a major effect of smoking on the risk of thromboembolism in a group of otherwise healthy women using oral contraceptives. The patients taking part in the study were all interviewed as part of a large, continuous drug surveillance programme. The details of their smoking habits and history of oral contraceptive use were taken as part of an extensive interview, and were recorded before the hypotheses at issue had been proposed. Therefore, it is highly unlikely that there was any bias when histories were taken, either for patients or controls.

Since there are considerable differences in the smoking habits of patients in different age groups, we took this factor into account by a matching procedure. The latter was also used to take into account any differences which could have arisen between the two sources of information which comprised the study population.

It is extremely unlikely that there were differences relating to smoking habits in the criteria used to make the diagnosis of thromboembolism or deep venous thrombosis within this set of oral contraceptive users. Moreover, since patients admitted with diseases related to smoking were excluded from the study, the smoking habits of the controls probably reflected the habits of communities from which they were drawn.

Our results suggest that the differences in the activities of the coagulation and fibrinolytic systems in smokers and non-smokers reported by Meade and his colleagues[6] are not major factors in the aetiology of uncomplicated venous thrombosis in women using oral contraceptives. These differences may be important, however, in explaining the proposed synergistic effect of smoking and oral contraceptive use on the risk of myocardial infarction in young women, which was recently reported by Mann *et al* in Oxford.[8]

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(*Accepted 29 July 1977*)

Lumbar epidural analgesia in labour in twin pregnancy

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British Medical Journal, 1977, **2**, 730-732

Summary

Fifty twin pregnancies in which the mother received epidural analgesia in labour were compared with 92 in which the mother received standard parenteral analgesia. The duration of the first and second stages of labour; the incidence of assisted deliveries when the head presented; the proportion of breech extractions when either the first or second twin presented by the breech; the incidence of low Apgar scores; and the perinatal mortality were not significantly different in the two groups.

These findings suggest that lumbar epidural analgesia is safe for providing pain relief in labour for patients with a twin pregnancy. Moreover, an epidural block is preferable to conventional analgesia in these cases as it allows prompt intervention to effect delivery of the second twin.

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Introduction

In singleton pregnancies the administration of epidural analgesia in labour is safe for both mother and fetus.[1] Its use in labour in patients with a twin pregnancy, however, is controversial. It