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Risk factors for recurrence of venous thromboembolism associated with the use of oral contraceptives☆,☆☆

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Abstract

Background: Combined oral contraceptives (COC) increase the risk of venous thromboembolism (VTE), but the risk of recurrent VTE is not precisely determined. In this retrospective cohort study, we sought the risk factors for recurrence after a first VTE that occurred in women taking COC.

Study Design: Time-to-event analysis was done with Kaplan–Meier estimates. In total, 172 patients were included (43% with pulmonary embolism): 82% had no other clinical risk factor for VTE.

Results: Among the 160 patients who stopped anticoagulation, the cumulative incidence of recurrent VTE was 5.1% after 1 year and 14.2% after 5 years. Significant factors associated with recurrence were renewed use of COC [hazard ratio (HR)=8.2 (2.1–32.2)], antiphospholipid syndrome [HR=4.1 (1.3–12.5)] and protein C deficiency or factor II G20210A [HR=2.7 (1.1–7)]. Pure-progestin contraception [HR=1.3 (0.5–3.0)] or factor V Leiden [HR=1.3 (0.5-3.4)] did not increase recurrence. Postsurgical VTE had a lower risk of recurrence [HR=0.1 (0.0–0.9)].

Conclusion: Further studies are warranted to determine whether testing for antiphospholipid syndrome, protein C deficiency or the factor II G20210A could modify the duration of anticoagulation. This study confirms the safety of pure-progestin contraception.

Keywords: Venous thromboembolism; Combined oral contraceptives; Recurrence

1. Introduction

In women who use combined oral contraceptives (COC), i.e., an oral contraceptive that contains progestin and estrogen, the risk of venous thromboembolism [VTE; deep venous thrombosis (DVT) and/or pulmonary embolism (PE)] is increased by 3 to 6 times compared with nonusers [1]. The incidence of VTE during the use of COC is approximately 30–40 per 100,000 user-years [1]. In young women of reproductive age, approximately one half of cases of VTE occur during COC use [2,3]. The risk is increased with an increased dose of estrogen, with a risk ratio of 1.6 between 30 mcg and 50 mcg of ethinylestradiol [4]. Several prospective studies including large cohorts [5,6] show that use of third-generation COC does not increase VTE risk when compared with second-generation COC. In contrast, other epidemiological and prospective studies including meta-analyses have shown an increased VTE risk following use of third-generation COC compared with second-generation COC (risk ratios varying from 1.3 to 1.7) [7–10]. A recent large cohort study confirmed these results and showed clearly that use of progestin-only pills does not carry an increased risk of VTE when compared with no use of OCs [11].

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However, little is known about the characteristics of patients who experience a first episode of VTE during COC use and about the risk factors for recurrence. A small study found that confirmed hereditary risk factors were present in all 15 enrolled patients [12]. Another study showed that VTE was less likely to recur when the patients stopped taking COC [13], but this study was conducted before the major thrombophilic conditions were recognized. Subgroups of women who were using COC during a first episode of VTE have been included in four large studies to assess the risk factors for recurrence [14–17]. However, in these studies, details about baseline characteristics and recurrence, e.g., the type of subsequent contraception or the number of pregnancies, are not given. In order to improve the management of VTE in women who use COC, it seems worthwhile to analyze a sample of such patients that is as homogeneous as possible. The objectives of the present study were to describe and analyze the baseline characteristics of a retrospective cohort of women from a single center and to assess possible risk factors for recurrence after a first VTE that occurred during the use of COC.

2. Methods and materials

2.1. Patients and study design

This retrospective cohort study was conducted on patients referred to a single center (the Federated Departments of Internal Medicine and Clinical Haematology, Clermont-Ferrand, France) from November 1, 1995, to December 31, 2008. These departments are a secondary or tertiary center for the treatment of VTE in a region of 1.34 million people (Auvergne, France). During this period, 1143 patients were referred for VTE, mainly to evaluate the duration of anticoagulation soon after an initial or recurrent event. Using the electronic hospital registry, all women who had had a first objectively confirmed episode of VTE during COC use or less than 1 month after discontinuation of COC were included in this study. Deep vein thrombosis was considered established when diagnosed by compression ultrasonography or venography. Objectively documented PE required ventilation and perfusion lung scanning, spiral computed tomographic scanning or pulmonary angiography. One hundred and seventy-two patients fulfilled these inclusion criteria. Clinical characteristics [including surgery, plaster cast, immobilization (>48 h), long distance air travel (>5000 km), tobacco use, being overweight (body mass index>25 kg/m^2), chronic inflammatory disease, family history and reproductive history] and biological data were collected in the medical file until the last visit (Table 1). Antiphospholipid antibody syndrome (APS) was defined as the presence of lupus anticoagulant and/or anticardiolipin antibody on two or more occasions at least 12 weeks apart. Between February 17, 2009, and April 5, 2009, the patients were interviewed by telephone in order to collect data on relevant clinical circumstances, such as trauma, immobility, use and type of OC, pregnancies and, if any, antithrombotic prophylaxis used during pregnancy and postpartum after the first VTE event. These data confirmed or completed data in the hospital medical file. The cohort was identified as women with VTE from electronic hospital registry from November 1, 1995, to December 31, 2008. The women could be eligible for this study after a first or a recurrent VTE event. The history of subsequent exposure to oral contraception and recurrent VTE was not always reported in hospital medical file, and the patients were interviewed by telephone to complete these data. These subsequent events were confirmed (e.g., use and type of oral contraception, recurrent thrombotic events, etc.) by the general practitioner medical file. If information from the hospital medical file and phone call were in conflict, the general practitioner medical file was also used. The recurrence of VTE was considered established using the same criteria as the first episode. The data on documented recurrent thrombotic events were collected from the hospital or general practitioner medical file. Thirty-one patients could not be interviewed because phone number and mail address were expired and their general practitioner also had no more contact too. For these patients (considered as "lost during follow-up" in statistical analysis), the possible recurrence period was recorded as the date of the last visit found in the medical file. The ethical committee of the country (Committee of People Protection=CPP VI, South-West, France) was consulted about this study. Given the retrospective, noninterventional method of this study, the CPP stated that its approval was unnecessary.

Table 1
Characteristics of the 172 patients at the first episode of VTE that occurred during the use of COC

Median age in years (range)	25.5 (17–53)
Type of VTE	
PE alone	45 (26%)
DVT alone	98 (57%)
PE+DVT	29 (17%)
VTE in at least one first-degree relative	38 (22%)
Median duration of COC use before VTE in months (range)	60 (1–336)
Overweight (body mass index>25 kg/m^2)	50 (29%)
Other reversible risk factors for VTE	
Surgery	12 (7%)
Plaster cast	8 (5%)
Immobilization (>48 h)	8 (5%)
Long distance air travel (>5000 km)	3 (1.7%)
Chronic inflammatory diseases	5 (3%)
Tobacco use	67 (39%)
Familial thrombophilia	
Factor V Leiden (170[a])	33 (19.2%)
Factor II G20210A (158[a])	12 (7%)
Protein S deficiency (169[a])	22 (13%)
Protein C deficiency (169[a])	11 (6.5%)
Antithrombin deficiency (168[a])	4 (1.2%)
APS (168[a])	13 (7.7%)
Hyperhomocysteinemia (162[a])	8 (4.9%)

[a] Number of patients in whom the test was performed.