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Full Length Article

Duration of oral contraceptive use and the risk of venous thromboembolism. A case-control study

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ABSTRACT

Introduction: Oral contraceptive (OC) use increases the risk of venous thromboembolism (VTE), but the effect of duration of use remains to be elucidated.
Patients and methods: This case-control study was aimed to investigate the duration of OC use on the risk of VTE according to women age, periods of use, prevalence of other risk factors and the role of thrombophilia abnormalities. Seven-hundred patients and 209 controls who used OC were stratified into short users (≤1 year), long users (1 to 5 years), and very long users (>5 years).
Results and conclusions: Compared to non-users, the odds ratio (OR) for VTE was 9.0 (95% CI 6.9–12.2) in short, 6.5 (95% CI 4.8–83.7) in long and 5.9 (95% CI 4.4–8.1) in very long users. The risk of VTE in short users was highest in women ≤30 years and in the first year of use (OR 13.1, 95% CI 7.7–22.4) and decreased afterward (OR 7.7, 95% CI 5.0–11.9). This trend was not observed in women >30 years. Compared to non-carriers and non-users, a joint effect of thrombophilia abnormalities and OC use on VTE risk was observed particularly in short users (OR 62.2, 95% CI 29.8–129.6), but also afterward (OR 25.4, 95% CI 16.5–39.2). Other transient risk factors for VTE were present in 25% of very long and 16% of short users. In conclusion, the risk of VTE in OC users decreases over time only before 30 years and in first users. Thrombophilia abnormalities strongly interact with the duration of OC use in determining VTE.

1. Introduction

Oral contraceptives (OC) are the most popular and efficacious contraception method worldwide. However, their use is associated with an increased risk of venous thromboembolism (VTE), that is attributable either to the dose of estrogen and the type of progestogen [1]. The use of OC increases the 0.5 to 1.0 per 10,000 person-years baseline incidence rate of VTE in women in childbearing age by a factor of approximately 6 or even more for preparations containing >30 μg of estrogen and progestogens other than levonorgestrel [2,3]. Although the incidence of VTE remains low, OC use has a strong impact on the thrombotic risk, being >100 million women who use OC worldwide [4]. The OC-related risk of VTE is particularly high in women with a baseline increased risk, e.g. carriers of thrombophilia abnormalities, and the two risk factors interact synergistically on the thrombotic risk [5–7]. Among women with VTE during childbearing age, the most common transient risk factor is OC use, recognized in approximately 60% of patients and inherited or acquired thrombophilia abnormalities are also frequently detected [8,9]. Being VTE a multifactorial disease, more than one risk factor is frequently recognized and it is important to weight each of them on an individual basis. Indeed, it is known that the risk of thrombosis in OC users is higher in the first 6–12 months of use and in those using OC for the first time, but whether this difference is present at any age and is mediated by the presence of thrombophilia abnormalities has not been elucidated yet [1,2,5].

Aims of this case-control study were to investigate the association between the duration of OC use and the risk of VTE according to the age and the periods of OC use, the prevalence of other risk factors for VTE in OC users and the role of thrombophilia abnormalities according to the duration of use.

2. Patients and methods

In this case-control study women of childbearing age (defined as the period of life between puberty and menopause when it is physically possible to conceive) referred to our Thrombosis Center for thrombophilia screening after a first episode of objectively confirmed

Abbreviations: OC, oral contraceptive; VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval.

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VTE between January 1994 and December 2014 formed the initial patients population. VTE included deep vein thrombosis of the lower limbs (diagnosed by compression ultrasound or venography), pulmonary embolism (V/Q lung scan, CT scan or pulmonary angiography) and cerebral vein thrombosis (cerebral digital angiography, CT angiography, magnetic resonance or magnetic resonance angiography). Women with pregnancy- or cancer-related VTE were excluded because pregnancy mutually excludes OC use and cancer is a strong independent risk factor for VTE [10]. Women with liver or renal diseases are not represented in our patients' population as their diseases affect most of the thrombophilia tests performed in plasma. The definition of liver and kidney disease was based on an existing diagnosis made by a specialist or abnormal liver or renal function tests. Healthy women of childbearing age, friends or partners of the whole population of the patients referred to our Center in the same study period, who voluntarily agreed to undergo thrombophilia testing, were selected as control group. Exclusion criteria for controls were pregnancy, overt neoplastic, autoimmune, liver or renal diseases at the time of blood sampling. Previous episodes of thrombosis were excluded by means of a validated questionnaire [11]. Information on OC use at the time of VTE for patients or blood sampling for controls, duration of use and previous periods of use were carefully collected, as well as the type of compound. OC were classified as first generation, containing lynestrenol or norethindrone/norethindrone acetate; second generation, containing levonorgestrel or norgestrel; third generation, containing desogestrel or gestodene; fourth generation containing the antimineralocorticoid drospirenone; those containing cyproterone acetate; others, containing dienogest or transdermal patches or hormone releasing intrauterine devices. Surgery, trauma and immobilization (plaster casts or prolonged bed rest >1 week) within a month preceding the event were considered transient risk factors for VTE. Events that occurred in the absence of the aforementioned risk factors were considered unprovoked. The study was approved by the Hospital Institutional Review Board and all patients and controls gave written informed consent to participate to the study.

2.1. Laboratory tests

Blood samples for thrombophilia testing were anticoagulated with sodium citrate (3.8% wt/vol) and taken after at least one month from VTE in patients and at the time of the visit in controls. Thrombophilia screening included: DNA analysis for the 1691 guanine to adenine substitution in coagulation factor V gene (factor V Leiden) [12] and for the 20210 guanine to adenine substitution in the 3′-untranslated region of the prothrombin gene [13] that are both gain-of-function mutations associated with hypercoagulability; functional and antigenic (when required) assays for plasma fibrinogen, antithrombin, protein C and protein S [14]; antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein IgG and IgM antibodies) [15]; plasma factor VIII, measured with one-stage coagulation bioassay using factor VIII-deficient plasma as substrate and the activated partial thromboplastin time as reagent [16]. High factor VIII plasma levels were defined when exceeding the 95th percentile of the distribution among controls (158 IU/dL). Plasma homocysteine was measured both at fasting and after a methionine load of 3.8 g per square-meter of body surface area, and HHcy was defined when levels exceeded the 95th percentile of the homocysteine distribution among controls (17 and 22 μmol/L fasting levels and 28 and 29 μmol/L the difference between post-methionine load and fasting levels, for women and men, respectively) [17].

Patients who were taking vitamin K-antagonists at the time of the first visit were asked to provide a second blood sample after discontinuation of oral anticoagulant therapy, because it affects measurements of protein C and protein S. The inheritance of antithrombin, protein C and protein S deficiency was confirmed on a second blood sample and in at least one relative.

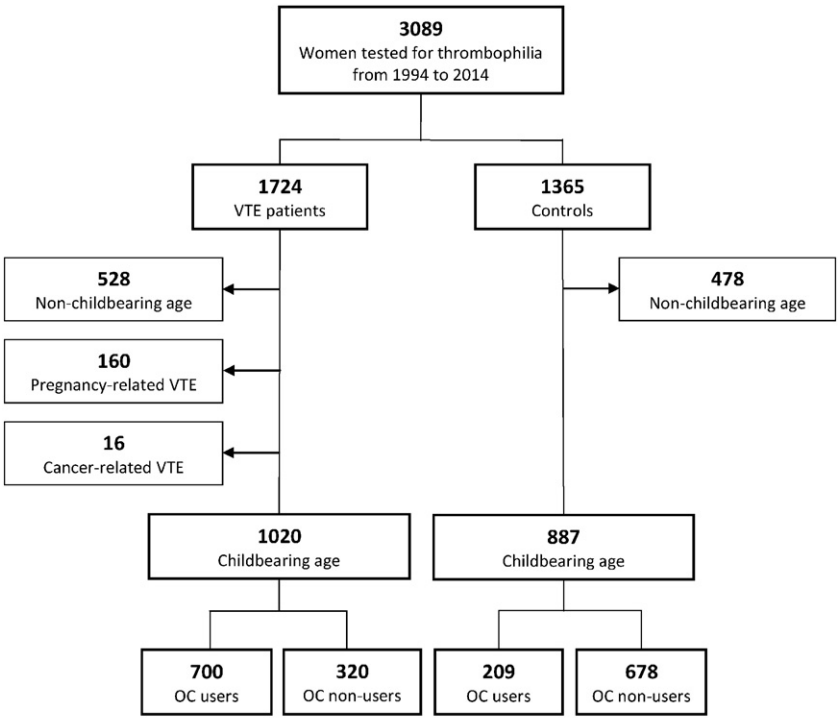

Fig. 1. Selection of the study population. VTE = venous thromboembolism OC = oral contraceptive.