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Hormonal contraceptives and venous thromboembolism: Are inflammatory bowel disease patients at increased risk? A retrospective study on a prospective database

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HIGHLIGHTS

- Contraceptives do not increase the risk of VTE in IBD patients in remission.
- Irrespective of baseline disease, smoking is associated with VTE.
- IBD patients receiving contraceptives should be encouraged to quit smoking.

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ABSTRACT

Recent studies showed an increased risk of venous thromboembolism (VTE) in patients receiving oral hormonal contraceptives. Inflammatory bowel diseases (IBD) often affect young patients and represent a pro-coagulant condition. This could result from active inflammation, but a potential role for genetic and molecular factors has been suggested. Hormonal contraceptives have also been associated with increased risk of VTE and the risk may be greater in IBD patients that already are in a pro-coagulant status, but no definitive data are available in this population. The purpose of our study was to seek for differences of the risk of VTE in IBD patients receiving hormonal contraceptives compared with controls.

This is a retrospective study. We interrogated a prospectively maintained database of IBD patients observed at our outpatient clinic between 2000 and 2014. All female patients managed conservatively, with no active disease, who were taking oral hormone contraceptives in the study period, were included. Patients observed for other-than-IBD conditions at our Unit and at the Unit of Gynaecology and Obstetrics, receiving contraceptives, served as controls (ratio 1:2). Patients with cancer, those receiving hormonal therapy, and those with known genetic predisposition to VTE were excluded.

We included 146 six IBD patients and 290 controls. One patient in each group developed VTE. Overall, the incidence of VTE associated with oral contraceptives was 0.5%. IBD was associated with increased risk of VTE (OR 1.9, 95% CI 0.12–32.12, $p > 0.99$). Active smokers since 10 years (17.2%) had higher risks of VTE (OR 8.6, 95% CI 1.16–19.25, $p = 0.03$).

Our data show that patients with IBD in remission are not at higher risk of VTE due to oral oestrogen-containing contraceptives compared with non-IBD controls. Smokers are at increased risk, irrespective of the baseline disease.

1. Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory

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conditions caused by complex etiopathogenetic mechanisms [1,2], which can affect patients at any age [3–8]. Crohn's disease (CD) and ulcerative colitis (UC) are the most common IBD. Patients suffering from IBD are at increased risk of venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE) [9,10]. VTE can result from active inflammation, but it has also been suggested that more complex mechanisms may underlie the increased risk observed in IBD patients [9–11].

It has been reported that oral oestrogen-containing contraceptives are associated with increased risk of VTE, in so much that thrombotic events in contraception users younger than the age of 20 years account for 5–10% of total contraception-related VTE events in population-based studies [12].

It could be hypothesized that IBD and hormonal contraceptives play a synergistic role in increasing the risk of VTE, but no studies are available concerning this hypothesis, especially in patients without active inflammation.

Our aim was to seek for differences of the risk of VTE in female IBD patients receiving oestrogen-containing contraception compared with age-matched non-IBD controls.

2. Materials and methods

We retrospectively interrogated a prospectively maintained database of IBD patients observed at our Centre between January 2000 and June 2014. All female patients seen at our outpatient clinic who were not operated on and had no active disease were evaluated for inclusion. We included in our study all fertile, female IBD patients who were taking oral oestrogen-containing contraceptives in the study period.

A comparison group of controls was established with patients observed for other-than-IBD conditions at our Unit and at the Unit of Gynaecology and Obstetrics (ratio 1:2) [13–20]. Demographics and physical information of patients were collected from the clinical charts. Patients were phoned to collect additional information.

Exclusion criteria were as follows: 1) patients with cancer [21–24], 2) patients with active disease, 3) patients with known genetic predisposition to VTE, 4) patients who received surgery, and 5) ongoing hormonal therapy or treatment with immunodepressants (control group) in the study period. Control group patients who had conditions needing ambulatory or day surgery who were not operated on or accessed the Hospital for diagnostic purposes.

Life-style confounders for VTE were taken into account. As an example, smoking and being inactive increases the risk of VTE. Specifically, all patients were phoned or asked during follow-up visits to report on their occupation and level of physical activity, as well as smoking habit and duration. Patients were classified as A) "active", if they had o physically demanding occupation, or if their leisure physical activities were equal or superior to 5/day per week., B) "moderately active", if their leisure physical activities were between 2 and 4 per day per week, and C) "sedentary" if they had a sedentary occupation and physical activities were below 1 per day per week This was made to disclose potential discrepancies between groups concerning factors that are associated with increased risk of VTE *per se*.

Outcome variable was the development of VTE while on oral hormonal contraceptive treatment. We sought for differences in the incidence of VTE in patients of both groups, and estimated the odds ratio (OR) associated with IBD in oral contraceptive receivers. A multivariate regression was run, in order to exclude potential confounders for VTE. OR is reported with 95% confidence intervals (95%CI). OR not including 1 and Fisher's exact test results with p values < 0.05 were considered statistically significant.

3. Results

One-hundred forty-six IBD patients (49 CD, 97 UC), median age 27 (range 19–41) years fit in the criteria and were included. One CD developed DVT while receiving contraceptives. The control group included 290 patients. One patient developed DVT. No cases of PE were observed. Overall, the incidence of VTE associated with oral contraceptives was 0.5%. Median follow-up length was 7.3 (range 1–15) years in IBD and 6.9 (range 1–14) in controls ($p = 0.81$).

Concerning baseline characteristics, the groups were similar (Table 1). Median age and median body mass index values were comparable. No differences were observed concerning patients classified as "active" (21 vs. 35), "moderately active" (46 vs. 82), and "sedentary" (79 vs 173, IBD vs controls, $p = 0.09$).

Baseline diseases of the control group were 1) benign coetaneous cysts (125), 2) groin or crural hernia ($n = 68$), and 3) minor vulvovaginal conditions ($n = 97$).

Patients with IBD were not at increased risk of VTE (OR 1.9, 95% CI 0.12–32.12, $p > 0.99$). Patients receiving immunosuppressant and biologic drugs showed a trend toward an increased risk of VTE (OR 5.6). This observation did not reach statistical significance ($p = 0.3$). When analysing patients who were active smokers since 10 years (17.2%), we found that this condition was significantly associated with an increased risk of VTE (OR 24.6, 95%CI 1.16–517.9, $p = 0.03$).

4. Discussion

In our study, we did not find an increased rate of VTE in female IBD patients in remission compared with non-IBD patients receiving oral hormonal contraceptives. Only two patients developed VTE overall, but prolonged exposure to tobacco smoking seemed to increase the odds of VTE, irrespective of the baseline disease.

CD and UC are the two principal IBD, which can affect people at any age and are characterised by a remitting-relapsing course [1–8,25–27], often requiring medical, surgical, or combined approaches [27–42]. Etiopathogenesis of IBD relies on complex interactions between autoimmune mechanisms and environmental factors, which have not been fully understood [1,25,26]. IBD patients are at increased risk of cancer [13,43–50], which is a risk factor for VTE, so we sought for malignancies and excluded such patients from the analysis.

In addition, IBD patients may suffer from extra-intestinal manifestations (EIMs), consisting of a plethora of accompanying symptoms and alterations occurring at organs not related to gastrointestinal tract. A pro-thrombotic status is observed in IBD patients, often accompanying active flares [9–11]. We hence removed from analysis patients with active IBD. The exact mechanism that leads to the increased risk of VTE in IBD patient is still to

Table 1
Characteristics of patients and outcome. Data are n (%) or median (range).

	IBD (n = 146)	Controls (n = 290)	*p*
Age, yr	26 (19–38)	27 (20–41)	>0.099
BMI, kg/m^2	22 (19–31)	22 (18–31)	>0.99
Occupation and lifestyle			0.09
- Active	21 (14.4)	35 (12)	
- Moderately active	46 (31.5)	82 (28.3)	
- Sedentary	79 (54.1)	173 (59.7)	
Venous thromboembolism			>0.99
- DVT	1 (0.7)	1 (0.3)	
- PE	0 (0)	0 (0)	

BMI: Body Mass Index; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism. IBD: Inflammatory Bowel Diseases.