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Absolute and Attributable Risk of Venous Thromboembolism in Women on Combined Cyproterone Acetate and Ethinylestradiol

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Abstract

Objective: To achieve absolute risk estimates of venous thromboembolism (VTE) among women on cyproterone acetate plus ethinylestradiol (CPA/EE), and on combined oral contraceptives (COCs).

Methods: From the Danish National Register of Patients (NRP), 1996 to 1998, the records of 1.1 million Danish women, ages 15 to 44 years, were searched for evidence of VTE. COC use was ascertained through mailed questionnaires. Sales statistics of COCs and CPA/EE were provided through Danish Drug Statistics.

Results: During the time frame of the study, 330 women were found to have had VTE while on COCs or CPA/EE. Of these women, 67 were on levonorgestrel-containing COCs and 11 were on PTA/EE. The corresponding absolute risk of VTE was 3.4 (range, 3.1–3.8) per 10 000 women years among the women on COCs, 4.2 (range, 3.2–5.2) per 10 000 women years among women on levonorgestrel-containing COCs, and 3.1 (range, 1.3–4.9) per 10 000 women years among the women on CPA/EE.

Conclusion: Our results suggest the absolute risk of VTE among Danish women on COCs is similar to that among women taking CPA/EE.

Résumé

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Key Words

Venous thromboembolism, cyproterone acetate, oral contraceptives, attributable risk, levonorgestrel

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INTRODUCTION

Some epidemiological studies have suggested an increased risk of venous thromboembolism (VTE) among current users of the anti-androgenic combination of cyproterone acetate (CPA, 2 mg) and ethinylestradiol (EE, 35 µg) or CPA/EE, over that among users of traditional combined oral contraceptives (COCs),[1,2] whereas other investigators have found the relative risks of VTE among CPA/EE users to be comparable with the risk among users of traditional COCs.[3,4]

The aim of this analysis was to provide absolute risk estimates of VTE among current users of CPA/EE as compared to users of COCs, and to calculate absolute risk differences (attributable risk) between users of these product groups.

METHODS

Since 1977, all discharge diagnoses from all hospitals in Denmark have been recorded in the National Register of Patients (NRP) together with the patients' corresponding personal identification

(CPR) numbers. In Denmark, all women with VTE are referred to hospital.

During the period of 1994 to 1998, we conducted a nationwide case-control study on COCs and VTE, including all 15- to 44-year-old women hospitalized with VTE. These women were identified in the NRP, and information about exposures and risk factors, including COCs, was obtained through mailed questionnaires.[4] Throughout the last 3 study-years of 1996 to 1998, information on any current use of CPA/EE was also collected. Total sale statistics on COCs and CPA/EE in Defined Daily Doses (DDD) were provided from the Danish Drug Statistics, and population figures from Statistics of Denmark. Women with VTE were allocated to the type of COCs they were currently using at the time of their VTE. Each of the three study years, 1200 controls between 15 and 44 years old were randomly selected from the National Register of Danish Citizens. The controls indicated the brand they were currently taking at the time they filled out the questionnaire. Both hospital in-patients and outpatients were included.

The diagnosis of VTE was confirmed by the woman herself, and validated through conducted venography or ultrasound examination for deep venous thrombosis and scintigraphic examinations for pulmonary embolism. Ninety-five percent of included cases had received anticoagulation therapy.

Women with previous thrombosis and pregnant women were excluded from the analysis. A 1-year match in age between cases and controls was ensured in the analysis. Other details on the methods are given in another primary publication.[4]

RESULTS

Approximately 1.1 million Danish women 15 to 44 years of age were diagnosed as having VTE (Table). The sales of all COCs, levonorgestrel-containing COCs, and CPA/EE are indicated in the Table.

There were 330 cases of VTE in current users of COCs during the study period, with a corresponding VTE incidence rate of 3.4 (range, 3.1–3.8) per 10 000 women years. The incidence of VTE in women on levonorgestrel-containing COCs was 67, corresponding to an incidence rate of 4.2 (range, 3.2–5.2) per 10 000 women years (Table). The incidence of VTE in women on CPA/EE was 11, with an absolute incidence rate of 3.1 (range, 1.3–4.9) per 10 000 women years.

The attributable risk of VTE among women on CPA/EE as compared with women on COCs was –0.3 (–1.8 to 1.1) per 10 000 women years. The attributable risk of VTE among women on levonorgestrel-containing COCs compared to all women on COCs was –1.1 (–1.9 to –0.3) per 10 000 women years.

TABLE

WOMEN ON COMBINED ORAL CONTRACEPTIVES (COCS) AND CPA/EE IN DENMARK 1996–1998 AND ABSOLUTE RISK OF VENOUS THROMBOEMBOLISM IN WOMEN ON COCS AND CPA/EE*

Exposed women	
Women 15–44 years old (average through the period)	1 096 079
Sale of COCs (DDD)	349 866 454
Women years of COCs	958 538
Sale of levonorgestrel-containing COCs (DDD)	58 684 332
Women years of levonorgestrel-containing COCs	160 779
Sale of CPA/EE (DDD)	13 021 288
Women years of CPA/EE	35 675
Absolute risk of VTE	
VTE in women on COCs	330
VTE per 10 000 women years on COCs (95% CI)	3.4 (3.1–3.8)
VTE in women on levonorgestrel-containing COC	67
VTE per 10 000 women years on levonorgestrel-containing COCs (95% CI)	4.2 (3.2–5.2)
VTE in women on CPA/EE	11
VTE per 10 000 women years on CPA/EE (95% CI)	3.1 (1.3–4.9)
Attributable risk of VTE per 10 000 women years	
Women on CPA/EE – risk of VTE in women on all COCs	–0.3 (–1.8–1.1)
Women on CPA/EE – risk of VTE in women on COCs with levonorgestrel	–1.1 (–1.9–0.3)

*COCs: combined oral contraceptives; CPA/EE: combination of cyproterone acetate 2 mg and ethinylestradiol 35 µg; DDD: defined daily doses; CI: confidence interval; VTE: venous thromboembolism.

DISCUSSION

The absolute risk of VTE in women on COCs of 3.4 per 10 000 exposure years is in line with a 3- to 4-fold increased risk above a baseline risk in young nonpregnant women of 1 per 10 000 women years.[5] The slightly higher absolute risk in women on levonorgestrel-containing COCs, as compared with all women on COCs, is due to a dose of EE that is on average higher in the former group.

According to our estimates, women on CPA/EE have the same absolute risk of VTE as women on conventional COCs, including women on levonorgestrel-containing COCs. Although our case series on CPA/EE was small (11 cases), the numbers are similar to the other published studies of CPA/EE.[1,2] The women in our study were unselected, except for exclusion of pregnant women and women with previous VTE. Adjustment for included confounders such as body mass index and family disposition did not change our findings.[4]

CONCLUSION

According to unselected data from Danish women with VTE, cyproterone acetate with ethinylestradiol confers the same absolute risk of VTE as other combined oral contraceptives.

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