Risk of venous thromboembolism in women with polycystic ovary syndrome: a population-based matched cohort analysis

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ABSTRACT

Background: There is an increased risk of venous thromboembolism among women taking oral contraceptives. However, whether there is an additional risk among women with polycystic ovary syndrome (PCOS) is unknown.

Methods: We developed a population-based cohort from the IMS LifeLink Health Plan Claims Database, which includes managed care organizations in the United States. Women aged 18–46 years taking combined oral contraceptives and who had a claim for PCOS (*n* = 43 506) were matched, based on a propensity score, to control women (*n* = 43 506) taking oral contraceptives. Venous thromboembolism was defined using administrative coding and use of anticoagulation. We used Cox proportional hazards models to assess the relative risk (RR) of venous thromboembolism among users of combined oral contraceptives with and without PCOS.

Results: The incidence of venous thromboembolism among women with PCOS was 23.7/10 000 person-years, while that for matched controls was 10.9/10 000 person-years. Women with PCOS taking combined oral contraceptives had an RR for venous thromboembolism of 2.14 (95% confidence interval [CI] 1.41–3.24) compared with other contraceptive users. The incidence of venous thromboembolism was 6.3/10 000 person-years among women with PCOS not taking oral contraceptives; the incidence was 4.1/10 000 person-years among matched controls. The RR of venous thromboembolism among women with PCOS not taking oral contraceptives was 1.55 (95% CI 1.10–2.19).

Interpretation: We found a 2-fold increased risk of venous thromboembolism among women with PCOS who were taking combined oral contraceptives and a 1.5-fold increased risk among women with PCOS not taking oral contraceptives. Physicians should consider the increased risk of venous thromboembolism when prescribing contraceptive therapy to women with PCOS.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. The National Institutes of Health criteria estimates its prevalence in the United States to be between 6% and 10%, while the Rotterdam criteria estimates the prevalence to be as high as 15%.[1] Although its cause is not entirely known, the diagnostic criteria include oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries.[2] Women often present with clinical manifestations of high androgen levels, including facial hair growth (hirsutism), acne vulgaris and hair loss on the scalp. Previous studies reported the prevalence of impaired glucose tolerance to be 31.1%–35.2% and the prevalence of type 2 diabetes to be 7.5%–9.8% among women with PCOS.[3,4] A recent consensus workshop reported that the prevalence of several known risk factors for cardiovascular disease (hypertension, diabetes, abdominal obesity, psychological factors, smoking, altered apoA1/ ApoB ratios) are doubled among women with PCOS compared with matched controls.[1,5]

Combined oral contraceptives are the mainstay treatment for PCOS. However, they are also known to elevate the risk of venous thromboembolism and cardiovascular disease.[6] To date, contraceptive studies involving women with PCOS have focused mainly on efficacy, evaluating the effect of combined oral contraceptives on the reduction of hirsutism and hyperandrogenism.[7,8] Two studies assessed the metabolic effects of combined oral contraceptives in PCOS, but these studies had small sample sizes and could not evaluate for cardiovascular events.[9,10]

Although women with PCOS have an increase in both cardiovascular risk factors and subclinical cardiovascular disease,[11] recent guidelines have concluded there are no data in the literature assessing the association between the use of oral contraceptives and cardiovascular disease among women with PCOS.[2] Because combined oral contraceptives are the mainstay

treatment, our objective was to determine whether women with PCOS taking combined oral contraceptives have a greater risk of venous thromboembolism compared with other contraceptive users. We also examined whether women with PCOS not taking oral contraceptives had an increased risk of venous thromboembolism compared with the general population.

Materials and methods

Data source

The IMS LifeLink Health Plan Claims Database contains paid claims data from over 102 managed care plans in the US. This database contains fully adjudicated medical and pharmacy claims for over 68 million patients, including inpatient and outpatient diagnoses and procedures (International Classification of Diseases, 9th Revision [Clinical Modification (ICD-9-CM)] in addition to retail and mail-order prescription records. The data are considered to be reasonably representative of US residents with private health insurance in terms of geography, age and sex, and these data have been previously used to evaluate the comparative safety of combined oral contraceptives.[12–14] The LifeLink database is subject to quality checks to ensure data quality and to minimize error rates.[15]

This study was approved by the University of Florida Gainsville Health Science Institutional Review Board.

Study population

The study period was May 1, 2001, to Dec. 31, 2009. Women between the ages of 18 and 46 years were included in the analysis. The inception cohort was based on exposure to one of the following combined oral contraceptives containing ≤ 0.035 mg ethinyl estradiol: desogestrel, drospirenone, levonorgestrel, norethindrone, norethindrone acetate, norgestimate or norgestrel.

Because we required a 1-year period for baseline covariate assessment, we excluded women who did not have 1 year of total enrolment in the IMS database. We also excluded women with a history of cancer, cerebrovascular disease, cardiovascular disease, venous thromboembolism or prior anticoagulation (warfarin and heparin). Censoring occurred at the outcome of venous thromboembolism, after a gap in combined oral contraceptive therapy of 30 or more days, discontinuation of enrolment, and the end of the study period. Because venous thromboembolism risk varies substantially between person-time exposed to and unexposed to combined oral contraceptives, the exposure cohort was limited strictly to exposed person-years to increase internal validity of the study and to reduce concern for confounding by contraceptive use.

For inclusion in the PCOS cohort (nested within the combined oral contraceptive cohort),

Table 1: Health care and combined oral contraceptive use at baseline		
Characteristic	Polycystic ovary syndrome*	Matched controls
Women, no.	43 506	43 506
Age, yr, mean	28.7	28.9
Health care use, % of women		
Admission to hospital	3.57	4.05
Emergency department visit	4.79	4.45
Physician office visit	51.31	50.08
Combined oral contraceptive use		
New user,† no. (%) of women	20 150 (46.32)	20 278 (46.61)
Prevalent user,‡ no. (%) of women	23 356 (53.68)	23 228 (53.39)
Prior time on combined oral contraceptives, mean, d	103	103
Total time on combined oral contraceptives, mean, d	201	202
Number of combined oral contraceptives products used in the past, mean	0.6	0.6
Combined oral contraceptive, % of women		
Desogestrel, μg ethinyl estradiol		
20	3.45	3.38
25	0.47	0.46
30	8.39	8.31
Drospirenone, μg ethinyl estradiol		
20	7.46	8.45
30	20.81	21.02
Levonorgestrel, μg ethinyl estradiol		
20	5.19	5.14
30	3.75	3.72
Triphasic	2.35	2.11
Norethindrone, μg ethinyl estradiol		
35	10.53	10.28
Norethindrone acetate, μg ethinyl estradiol		
20	4.60	4.48
30	2.74	2.66
35	1.51	1.55
Norgestimate, ethinyl-estradiol μg		
25	5.78	5.68
35	18.31	18.21
Norgestrel, μg ethinyl estradiol		
30	4.66	4.55

*Defined as a claim for polycystic ovary syndrome (International Classification of Disease, 9th Revision [Clinical Modification (ICD-9-CM)] 256.4).
†Initiated combined oral contraceptive therapy after the polycystic ovary syndrome claim.
‡Evidence of combined oral contraceptive use during the 365-day period before the polycystic ovary syndrome claim.

women were also required to have a diagnosis of PCOS (ICD-9-CM 256.4). The index date was the first dispensing for a combined oral contraceptive after the PCOS claim. Those with combined oral contraceptive use during the 365-day period before the index date were considered to be prevalent users, while we considered women with no prior combined oral contraceptive use to be new users. We used a logistic regression model to develop a propensity score as the probability for developing PCOS. This score was formed from prescription and medical claims, demographics and health care utilization data during the 365 days before the index date, in addition to the calendar year of diagnosis (formed from covariates at cohort entry in Table 1 and Table 2). This technique is commonly used in large database studies to adjust for a large number of covariates without loss of statistical precision. A 1:1 matching technique, based on the propensity score, was used to select a comparator group of women without PCOS with similar baseline comorbidities (who were also taking combined oral contraceptives).

Outcome measure

The outcome of nonfatal venous thromboembolism was a combined outcome of pulmonary embolism (ICD-9-CM 414.1) and deep vein thrombosis (ICD-9-CM 453, 451.1). Cases were women who had an event during or within 30 days after cessation of combined oral contraceptive therapy. We included this 30-day window to avoid informative censoring bias, where women may stop taking combined oral contraceptives after having a venous thromboembolism.[16] All cases were also required to initiate anticoagulant treatment, with the first dose administered within 14 days of the venous thromboembolism claim. The case index date was 14 days after the venous thromboembolism claim to account for the anticoagulant assessment. This approach to identifying venous thromboembolism cases using subsequent anticoagulation therapy has been previously shown to have a 99% positive predictive value.[17]

Statistical analysis

In the primary analysis, we used Cox proportional hazards models to estimate the hazard ratio (HR) for venous thromboembolism. We performed a secondary analysis to model the association between PCOS and venous thromboembolism using a modified Poisson regression with a robust error variance, resulting in a risk ratio (RR).[18]

We performed a secondary analysis with a more inclusive definition of PCOS to improve sensitivity and to evaluate the impact of including PCOS diagnostic criteria and treatment in

our case ascertainment. Women with a claim for PCOS (ICD-9-CM 256.4), a claim for a diagnostic criteria (anovulation [ICD-9-CM 628.0] and hirsutism [ICD-9-CM 704.1]), or a prescription for antiandrogen treatment (i.e., spironolactone) were included as having PCOS. Spironolactone was included as a proxy for the

Table 2: Comparison of medication use and comorbidities at cohort entry and study end

Variable	Cohort entry		Study end	
	PCOS*	Matched controls	PCOS*	Matched controls
Medication use, % of women				
ACE inhibitor or ARB	2.18	2.57	5.06	5.10
Beta blocker	3.42	3.52	7.95	6.80
Benzodiazepine	8.93	8.06	20.77	16.95
Calcium-channel blocker	0.92	1.06	2.51	2.18
Diabetes medications	20.31	20.65	42.88	21.55
SSRI or tricyclic antidepressant	17.09	17.32	31.76	28.88
Statin or fibrate	2.45	2.79	5.79	5.23
Comorbidities, % of women				
Acne	11.04	10.92	24.15	19.65
Asthma	6.93	6.92	15.32	12.82
COPD	3.34	3.45	11.45	9.29
Diabetes	6.70	8.31	14.87	12.23
Dysmenorrhea	5.79	5.71	14.23	10.95
Endometriosis	2.71	2.82	7.42	4.88
Hyperlipidemia	10.47	10.91	27.10	20.15
Hypertension	7.82	8.40	18.70	14.75
Hypothyroid	8.23	8.32	17.23	12.67
Ovarian inflammation	1.74	1.83	5.72	3.84
Vaginal inflammation	12.56	12.52	31.22	27.64
Uterine leiomyoma	2.05	2.03	5.96	4.65
Irregular menstrual cycle	40.04	40.06	72.07	54.15
Migraine	5.53	5.67	15.10	12.33
Mood or anxiety disorder	15.96	16.26	34.09	29.65
Obesity	13.35	13.32	33.11	21.04
Peptic ulcer disease	0.40	0.42	1.32	1.03
Premenstrual tension syndrome (PMS or PMDD)	1.42	1.34	4.12	2.97
Sleep disorder	0.82	0.88	3.26	1.98
Smoking	2.57	2.71	7.31	6.85

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker, COPD = chronic obstructive pulmonary disorder, PCOS = polycystic ovary syndrome, PMDD = premenstrual dysphoric disorder, PMS = premenstrual syndrome, SSRI = selective serotonin reuptake inhibitor.
*Defined as a claim for PCOS (International Classification of Disease, 9th Revision [Clinical Modification (ICD-9-CM)] 256.4).

treatment of hyperandrogenism and not as an independent risk factor for venous thromboembolism. As in the main analysis, we used a 1:1 match, based on a propensity score to predict having PCOS to select a comparator population, and we used Cox proportional hazard models to estimate the association between PCOS and venous thromboembolism. All additional PCOS criteria were also evaluated in similar separately matched analyses.

Comparison with women with PCOS not using combined oral contraceptives

We did not conduct a direct comparison of the risk of venous thromboembolism among women with PCOS using, compared with those not using, combined oral contraceptive therapy; if the decision to treat or not to treat PCOS with combined oral contraceptives is an indication of disease severity, then this analysis would be subject to confounding by indication.

To provide an assessment of baseline venous thromboembolism risk among women with PCOS compared with women without this syndrome, we obtained a random sample of 2 million women not taking combined oral contraceptives. We repeated all analyses as described above, with the exception that a 1:4 match was conducted to ensure adequate power based on the lower prevalence of PCOS among women who do not use combined oral contraceptives.

We evaluated proportionality of hazards using the log–log survival curve.

Results

We included 1 632 678 combined oral contraceptive users who met our inclusion criteria. Of these, 46 867 women (2.9% of the total population) had a claim for PCOS. We were able to successfully match 43 506 (92.8%) of these women,

producing a patient population of 87 012 for our primary analysis.

We matched women based on comorbidities, assessed during the one year before a claim for PCOS, creating populations with nearly identical characteristics at cohort entry (Table 1). Women with a PCOS claim, however, were more likely to develop nearly every study covariate after baseline, when compared with the matched controls (Table 2). Noteworthy differences at study end include the use of diabetic medications (PCOS: 42.88% v. controls: 21.55%), despite similar rates of diabetes (14.87% v. 12.23%, respectively), hyperlipidemia (27.10% v. 20.15%, respectively), hypertension (18.70% v. 14.75%, respectively), menstrual irregularity (72.07% v. 54.15%, respectively) and obesity (33.11% v. 21.04%, respectively).

The incidence of venous thromboembolism among women with PCOS was 23.7/10 000 person-years, while that for matched controls was 10.9/10 000 person-years. Women with PCOS who were taking combined oral contraceptives had an HR for venous thromboembolism of 2.14 (95% confidence interval [CI] 1.41–3.24). Our secondary analysis found an RR of 2.12 (95% CI 1.40–3.21) (Table 3).

In our sensitivity analysis, a more inclusive definition of PCOS also included women who met a diagnostic criteria for PCOS (anovulation or hirsutism) or treatment for PCOS (spironolactone). The characteristics of this population are shown in Appendix 1 (available at www.cmaj.ca/lookup /suppl/doi:10.1503/cmaj.120677/-/DC1). This analysis included 89 555 women (5.5% of the total population) with PCOS, and 84 632 (94.5%) were successfully matched, defining a second cohort with 169 264 women. In this second analysis, the incidence of venous thromboembolism among women with PCOS was 24.1/10 000 person-years, while that for matched controls was 10.8/10 000 person-years. In this analysis, women with PCOS who were taking combined oral contraceptives had an HR for venous thromboembolism of 2.24 (95% CI 1.62–3.10) and an RR for venous thromboembolism of 2.23 (95% CI 1.61–3.08). In the stratified analyses, all additional measures of PCOS in this inclusive definition demonstrated increased risk of venous thromboembolism: anovulation HR 1.72 (95% CI 0.75–3.98), hirsutism HR 2.49 (95% CI 1.35–4.59) and spironolactone HR 1.89 (95% CI 1.15–3.10).

The incidence of venous thromboembolism was 6.3/10 000 person-years among women with PCOS not taking contraceptives, while the incidence among matched controls was 4.1/10 000 person-years. Among women not taking combined oral contraceptives, women with PCOS

Table 3: Risk of venous thromboembolism associated with PCOS in women taking the combined oral contraceptive pill

Variable	Cox proportional hazards models	Relative risk regression
PCOS claim	2.14 (1.41–3.24)	2.12 (1.40–3.21)
Composite PCOS definition*	2.24 (1.62–3.10)	2.23 (1.61–3.08)
PCOS symptoms and treatment		
Anovulation	1.72 (0.75–3.98)	1.70 (0.75–3.89)
Hirsutism	2.49 (1.35–4.59)	2.43 (1.30–4.56)
Spironolactone	1.89 (1.15–3.10)	1.86 (1.14–3.03)

Note: PCOS = polycystic ovary syndrome.
*Claims for PCOS, anovulation, hirsutism, spironolactone treatment, or PCOS-related procedures.

had an HR for venous thromboembolism of 1.55 (95% CI 1.10–2.19) and a RR of 1.63 (95% CI 1.13–2.34) compared with matched controls. The characteristics of this population are shown in Appendix 2 (available at www.cmaj.ca/lookup /suppl/doi:10.1503/cmaj.120677/-/DC1).

Interpretation

We found a 2-fold increased risk of venous thromboembolism among women with PCOS taking combined oral contraceptives compared with matched controls. We found a similar increased risk when we expanded the definition of PCOS by including its symptoms and treatment. We also found a 1.5-fold increased relative risk of venous thromboembolism among women with PCOS who were not taking contraceptives compared with matched controls.

Our findings are consistent with the previously reported 2-fold increase in most of the risk factors for venous thromboembolism among women with PCOS.[1] Among users of combined oral contraceptives, the incidence of venous thromboembolism for matched controls was comparable to that of users in the general population (7–11/10 000 person-years),[17,19] while the incidence among women with PCOS was doubled. Similarly, among women not using oral contraceptives, the incidence of venous thromboembolism among those without PCOS was close to previously reported baseline rates,[17] while those with PCOS had increased risk. The absolute rate of venous thromboembolism among women with PCOS taking combined oral contraceptives (23.7/10 000 person-years) was substantially higher than that among women with this condition not taking contraceptives (6.3/10 000 person-years).

Although the covariates at cohort entry were nearly identical between the groups, women with PCOS were more likely to experience nearly every comorbidity during follow-up. Covariates reported at end of the study had a longer period of assessment and thus were better captured; however, the differential development of these conditions supports the finding that women with PCOS are at risk of many additional comorbidities.[1]

The use of contraceptive products by women with PCOS is thought to improve cycle regulation and benefit both acne and hyperandrogenism.[20] Previous studies have found that combined oral contraceptives are effective for the reduction of androgen levels and hirsutism in women with PCOS; these studies have mainly focused on drospirenone, desogestrel and cyproterone acetate.[8,9,19] These studies were small in size and not powered to assess thrombotic events.

Limitations

Because combined oral contraceptives are routinely used by women with PCOS and these drugs are known to increase the risk of venous thromboembolism, including only users of these drugs limits both confounding by indication and contraindication. However, we do not have an accurate measure for many potential confounders (e.g., diet, exercise and family history of venous thromboembolism), and some residual confounding is likely present. Claims for obesity were similar between women with (13.35%) and without (13.32%) PCOS at study entry, suggesting that unmeasured obesity would not be different between groups; however, we did not have access to body mass index values, and residual confounding is possible.

Polycystic ovary syndrome is diagnosed based on the presence of 2 of the following 3 symptoms: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries.[1] This regimented clinical diagnostic criteria likely makes a claim for PCOS very specific, reducing potential bias from exposure misclassification. However, the sensitivity and specificity of PCOS claims are unknown, and the use of ICD-9-CM codes to identify participants with PCOS may underreport the true prevalence of this condition. Thus, we developed a second definition based on diagnostic criteria and medication treatment in order to perform a second analysis with an improved sensitivity. This inclusive definition gave a prevalence of PCOS of 5.5% in the study population, which is comparable to the known prevalence of 6%–10%, as defined using the National Institute of Health criteria.

Conclusion

Women with PCOS taking combined oral contraceptives had a 2-fold increased risk of venous thromboembolism, while such women not taking these drugs had a 1.5-fold increased risk. This is consistent with previous finding of increased cardiovascular risk factors and subclinical vascular disease among women with this syndrome.[1,5] Physicians should be aware of a potentially synergistic increase in venous thromboembolism risk in women with PCOS taking combined oral contraceptives.

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