

Epidemiology of Pregnancy-associated Venous Thromboembolism: A Population-based Study in Canada

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Abstract

Objective: To estimate the frequency of, and to identify risk factors for, pregnancy-associated venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) requiring hospitalization.

Methods: We conducted a population-based cohort study (N = 3 852 569) using the Discharge Abstract Database of the Canadian Institute for Health Information (CIHI), for the fiscal years 1991–1992 to 2005–2006. All women with pregnancy-related hospitalizations in Canada (excluding Quebec and Manitoba) were identified. DVT and PE rates were calculated using the number of hospital deliveries (i.e., cohort of women at risk) as the denominator for the antepartum and peripartum (labour and delivery) hospitalizations and for postpartum readmissions. Risk factors for DVT/PE were identified using logistic regression.

Results: During the antepartum, peripartum, and postpartum periods, 5.4, 7.2, and 4.3 VTE cases per 10 000 pregnancies, respectively were observed. The total incidence of DVT was 12.1 per 10 000 pregnancies (0.26 deaths per 100 000), and the rate for PE was 5.4 per 10 000 (0.96 deaths per 100 000). The strongest risk factors for DVT occurrence during the peripartum period were thrombophilia (adjusted odds ratio [aOR] 15.4; 95% CI 10.8–22.0), a past history of circulatory disease, and major

puerperal infection, whereas those for PE were previous DVT (aOR 56.9; 95% CI 40.9–79.1), heart disease (aOR 43.4, 95% CI 35.0–53.9), antiphospholipid syndrome, past history of circulatory disease, transfusion, and major puerperal infection.

Conclusion: Cases of VTE and associated deaths occur most frequently during the peripartum period. Although mortality from pregnancy-associated VTE is low, maternal characteristics and other factors can be used to identify women at risk for VTE.

Résumé

Objectif : Estimer la fréquence de la thromboembolie veineuse associée à la grossesse (TEV) [y compris la thrombose veineuse profonde (TVP) et l'embolie pulmonaire (EP) nécessitant une hospitalisation] et en identifier les facteurs de risque.

Méthodes : Nous avons mené une étude de cohorte en population générale (N = 3 852 569) en utilisant la Base de données sur les congés des patients de l'Institut canadien d'information sur la santé (ICIS), et ce, pour les exercices financiers 1991-1992 à 2005-2006. Toutes les femmes ayant été hospitalisées pour une raison associée à la grossesse au Canada (exception faite du Québec et du Manitoba) y ont été identifiées. Les taux de TVP et d'EP ont été calculés en utilisant le nombre d'accouchement à l'hôpital (c.-à-d. la cohorte de femmes exposées à des risques) à titre de dénominateur pour ce qui est des hospitalisations antepartum et peripartum (travail et accouchement), et des réhospitalisations postpartum. Les facteurs de risque de TVP/EP ont été identifiés au moyen d'une régression logistique.

Résultats : Au cours des périodes antepartum, peripartum et postpartum, 5,4, 7,2 et 4,3 cas de TEV par 10 000 grossesses ont été constatés, respectivement. L'incidence totale de la TVP était de 12,1 par 10 000 grossesses (0,26 décès par 100 000) et le taux d'EP était de 5,4 par 10 000 (0,96 décès par 100 000). Les facteurs de risque les plus influents, en ce qui concerne la survenue d'une TVP au cours de la période peripartum, étaient la

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thrombophilie (rapport de cotes corrigé [RCc], 15,4; IC à 95 %, 10,8–22,0), des antécédents de troubles du système circulatoire et une importante infection puerpérale, tandis que ceux qui étaient associés à l'EP étaient un antécédent de TVP (RCc, 56,9; IC à 95 %, 40,9–79,1), une maladie cardiaque (RCc, 43,4; IC à 95 %, 35,0–53,9), le syndrome des antiphospholipides, des antécédents de troubles du système circulatoire, une transfusion et une importante infection puerpérale.

Conclusion : Les cas de TEV et les décès qui leur sont associés surviennent le plus fréquemment au cours de la période peripartum. Bien que la mortalité attribuable à la TEV associée à la grossesse soit faible, les caractéristiques maternelles et d'autres facteurs peuvent être utilisés pour identifier les femmes courant un risque de TEV.

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INTRODUCTION

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, remains an important cause of maternal mortality and severe maternal morbidity, despite recent advances in thromboprophylaxis. Pulmonary embolism continues to be one of the most common causes of maternal death following childbirth in developed countries including Canada, the United States, and the United Kingdom.^{1–4} In addition to the mortality and short-term morbidity, women who have experienced venous thromboembolism during pregnancy may develop long-term sequelae that are associated with post-thrombotic syndrome, ranging from edema and skin changes to recurrent thromboses and ulceration.^{5–9} Pregnant women, in general, are four to five times more likely to develop venous thromboembolism than women who are not pregnant.^{9–19} This predisposition of pregnant women is attributed to the hypercoagulable state of pregnancy that protects women from hemorrhage during miscarriage and delivery.

Important issues concerning the natural history and prophylaxis/therapy of DVT and PE remain unresolved. Data from the United States, Denmark, and the United Kingdom describing trends in the incidence of pregnancy-associated VTE provide conflicting findings,^{14–17} and reported rates and risk factors vary widely.^{13–29} There are no national reports from Canada on current trends in rates of pregnancy-associated DVT and PE.

Although rates of maternal mortality and severe maternal morbidity in Canada are extremely low, obstetrical pulmonary embolism remains a serious issue and was responsible for 17% (55 of 324) of direct maternal deaths from 1981 to 2004.³⁰ Venous thromboembolism also complicates low-risk pregnancies in the postpartum period, with the risk of VTE being 2.2-fold higher after planned Caesarean section than after planned vaginal delivery.³¹ We carried out a study to estimate the incidence of pregnancy-associated VTE and the associated mortality, and to identify risk factors for VTE with a focus on pulmonary embolism.

MATERIALS AND METHODS

This study was based on hospital admission and separation records collated by the Canadian Institute for Health Information from fiscal year 1991–1992 to 2005–2006. The hospital records in the Discharge Abstract Database used for this study included approximately 70% of all hospitalizations of pregnant women for medical and obstetric reasons in Canada during the period of study. The records from the remaining 30% of hospitalizations were not included because complete information for the provinces of Quebec and Manitoba was not collected by CIHI. The total number of deliveries included in the study was 3 852 569. These deliveries represented approximately 98% of all deliveries eligible for inclusion in the study, because 98% to 99% of deliveries in Canada occur in hospital.^{32,33}

Hospital medical archivists extracted hospital discharge data including sex, age, date of admission, home postal code, province of hospital delivery, date and status at discharge, principal diagnosis, up to 15 secondary diagnoses (coded according to the International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9 CM] or the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada [ICD-10 CA]), and up to 10 diagnostic, therapeutic and surgical procedures (coded according to the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures or the Canadian Classification of Health Interventions). All corresponding ICD-10 CA codes used were mapped from the appropriate ICD-9 CM codes. Information in the database has been previously validated and extensively used in research and perinatal health surveillance.^{30,31}

We first searched the Discharge Abstract Database's hospitalization records for all pregnancy-associated VTE cases. DVT cases were identified using ICD-9 codes 451, 452, 453, 671.3, 671.4, and 671.5 or ICD-10 codes I80, I81, I822, I823, 0223, 0225, 0228, 0871 and 0873; PE cases were defined by ICD-9 codes 415.1, 673.2, 673.8 or ICD-10 codes I269, 0882, and 0888. All antepartum and peripartum (i.e., labour and delivery) hospitalizations and postpartum

ABBREVIATIONS

aOR	adjusted odds ratio
aRD	adjusted risk difference
CIHI	Canadian Institute for Health Information
DVT	deep vein thrombosis
PE	pulmonary embolism
VTE	venous thromboembolism

Table 1. Pregnancy-associated VTE incidence (per 10 000 women), mortality (per 100 000 women), and case fatality (per 1000 cases) by pregnancy period, Canada (excluding Quebec and Manitoba), 1991–2005

Period	Pregnant women	DVT			PE		
		Incidence	Mortality	Case fatality	Incidence	Mortality	Case fatality
Antepartum admission	3 852 569	3.9 (1493)	0.10 (4)	2.7	1.7 (667)	0.18 (7)	10.5
Peripartum hospitalization	3 852 569	5.4 (2089)	0.05 (2)	1.0	2.0 (768)	0.60 (23)	29.9
Postpartum readmission	3 852 569	2.8 (1095)	0.10 (4)	3.7	1.8 (679)	0.18 (7)	10.3
Total	3 852 569	12.1 (4677)	0.26 (10)	2.1	5.4 (2114)	0.96 (37)	17.5

readmissions were identified and defined as follows: antepartum hospitalizations included records with a pregnancy-related ICD code, with a fifth digit indicating a antepartum condition (e.g., ICD-9 codes 630–648 plus fifth digit “3”) and which did not include an obstetrical delivery code; peripartum hospitalizations were identified by well-defined ICD codes indicative of childbirth²⁹; and postpartum hospitalizations included records with a pregnancy-related ICD code with a fifth digit indicating a postpartum condition (e.g., ICD-9 codes 660–670, plus fifth digit “4”) that did not include an obstetrical delivery code (i.e., separate hospitalization following delivery). Covariates (i.e., maternal characteristics, pregnancy complications, and obstetric conditions) were also identified from the database, and most of them were defined using ICD codes (e.g., heart disease was defined by ICD-9 codes 390–398 and 421–429). To better estimate the frequency of VTE occurrence, subsequent admissions for VTE for the same individual were excluded from the analysis. We calculated rates of VTE in each of three periods (antepartum, peripartum, and postpartum) by conceptualizing a cohort of women at risk for VTE events, i.e., the number of hospital deliveries served as the denominator for calculating the incidence and mortality rates for the three respective periods. Rates were expressed per 10 000 or 100 000 delivering women. Because of the extremely low frequency of maternal mortality from VTE, we estimated three-year moving averages to obtain a temporal trend in VTE-associated mortality rates over the 15 years of study. Independent risk factors for DVT and PE were identified using logistic regression, and relationships were expressed using unadjusted and adjusted (for all covariates) odds ratios and 95% confidence intervals.

The database used for this study was a denormalized version of the Discharge Abstract Database prepared under strict confidentiality guidelines by CIHI, and accessible at the Public Health Agency of Canada. Individual consents

were not obtained from the patients whose data are contained in the database, and ethics review board approval was not required by either CIHI or the Public Health Agency of Canada.

RESULTS

Over the 15 years, 4677 women developed a DVT and 2144 a PE (239 had both DVT and PE), resulting in an incidence throughout pregnancy and the postpartum period of 12.1 per 10 000 women for DVT and an incidence of 5.4 per 10 000 women for PE. Most of the DVT and PE events occurred during the peripartum hospitalization, with incidences of 5.4 and 2.0 per 10 000 women, respectively. Overall mortality from PE was significantly higher than from DVT, and most deaths from PE occurred during the peripartum period (23 out of 37). Overall case fatality was 17.5 per 1000 cases for PE and 2.1 per 1000 for DVT (Table 1).

Temporal trends in pregnancy-associated DVT and PE rates showed contrasting patterns. The incidence of DVT decreased from 13.4 per 10 000 women in fiscal year 1991–1992 to 10.2 per 10 000 women in fiscal year 2005–2006, while PE incidence increased from 4.6 per 10 000 to 6.7 per 10 000 over the same period (Figure 1). The overall VTE-associated mortality rate (3-year moving average) showed a dramatic increase, from 0.4 per 100 000 pregnancies in 1991–1992 to 1.5 per 100 000 in 1995–1996, and a decrease thereafter to 0.6 per 100 000 (Figure 2).

Table 2 shows the numbers and rates of women who developed DVT or PE during peripartum hospitalization according to time period, region, and other characteristics. Elderly primigravidity and grand multiparity were associated with higher rates of both PE and DVT. The rate of DVT among peripartum women was essentially stable (5.4 per 10 000 in 1991 and 5.3 per 10 000 in 2005), while rates of PE doubled from 1.3 per 10 000 in 1991 to 2.6 per 10 000 in 2005. Maternal age was associated with VTE occurrence during

Figure 1. Trends in pregnancy-associated VTE occurrence (per 10 000 women), during antepartum, peripartum, and postpartum periods, Canada (excluding Quebec and Manitoba), 1991 to 2005

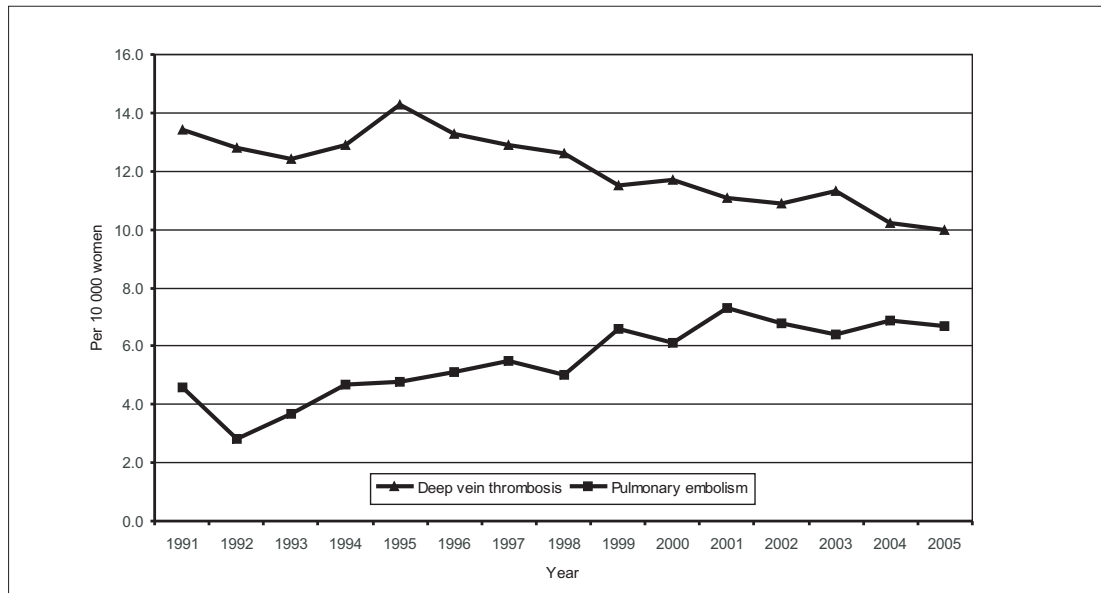
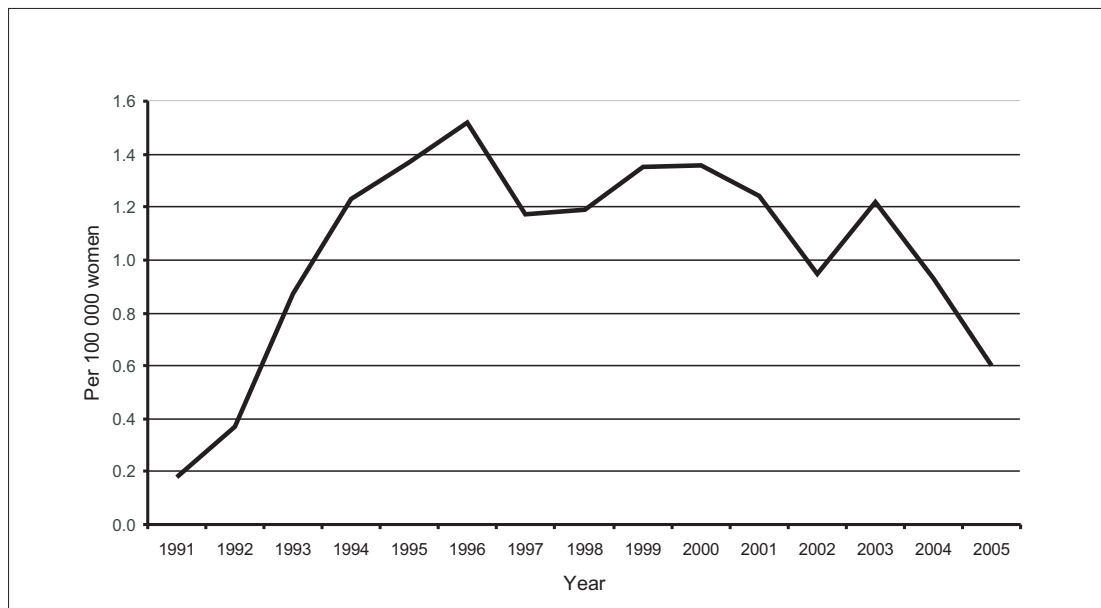


Figure 2. Trends in mortality rates (3-year moving average expressed per 100 000 women) from pregnancy-associated VTE, Canada (excluding Quebec and Manitoba), 1991 to 2005



Data points represent a 3-year moving average (e.g., rate for 1992–1993 was based on numbers for 1991/1992, 1992/1993, and 1993/1994) except for fiscal years 1991/1992 and 2005/2006, which were based on data for 2 years only.

pregnancy and postpartum. VTE rates during peripartum hospitalization increased with advancing age, while VTE rates were higher for both younger and older women during the antepartum and postpartum hospitalizations, and when the three periods were combined. For example, younger women were more likely to be hospitalized for VTE during the postpartum period (7.4 cases per 10 000 among women aged < 20 years and 7.0 cases per 10 000 among women aged ≥ 40 years vs. 3.8 cases per 10 000 for women aged 30

to 34 years) (Figure 3). The crude odds ratio for DVT during peripartum hospitalization comparing women aged ≥ 35 years with those < 35 years was 1.4 (95% CI 1.3–1.6); the crude odds ratio for PE in women aged ≥ 35 years compared with those < 35 was 1.5 (95% CI 1.3–1.8).

The rates of DVT and PE among women with and without specific risk and protective factors and the corresponding odds ratios derived from logistic regression are shown in Tables 3 and 4. Major risk factors for PE during the

Table 2. Numbers and rates of women who were diagnosed with DVT or PE by background characteristic during peripartum hospitalization in Canada, excluding Quebec and Manitoba (N = 3 852 569), 1991 to 2005

Characteristic	Numbers of DVT (per 10 000 deliveries)	Numbers of PE (per 10 000 deliveries)
Period		
1991/92–1993/94	442 (5.4)	108 (1.3)
1994/95–1996/97	455 (5.7)	134 (1.7)
1997/98–1999/00	386 (5.1)	143 (1.9)
2000/01–2002/03	411 (5.6)	192 (2.6)
2003/04–2005/06	395 (5.3)	191 (2.6)
Region		
Atlantic	175 (5.3)	46 (1.4)
Ontario	1146 (5.5)	457 (2.2)
West	761 (5.4)	262 (1.9)
Yukon, Nunavut, and Northwest Territories	7 (3.2)	3 (1.4)
Maternal age, years		
< 20	101 (4.5)	25 (1.1)
20–24	301 (4.4)	123 (1.8)
25–34	1281 (5.4)	463 (1.9)
35–39	332 (6.9)	332 (2.6)
≥ 40	74 (9.1)	33 (4.1)
Elderly primigravida*		
Yes	38 (10.5)	13 (3.6)
No	2051 (5.4)	755 (2.0)
Grand multipara†		
Yes	10 (9.8)	6 (5.9)
No	2079 (5.4)	762 (2.0)

*First pregnancy at ≥ 35 years of age.

†Having had ≥ 5 previous viable pregnancies.

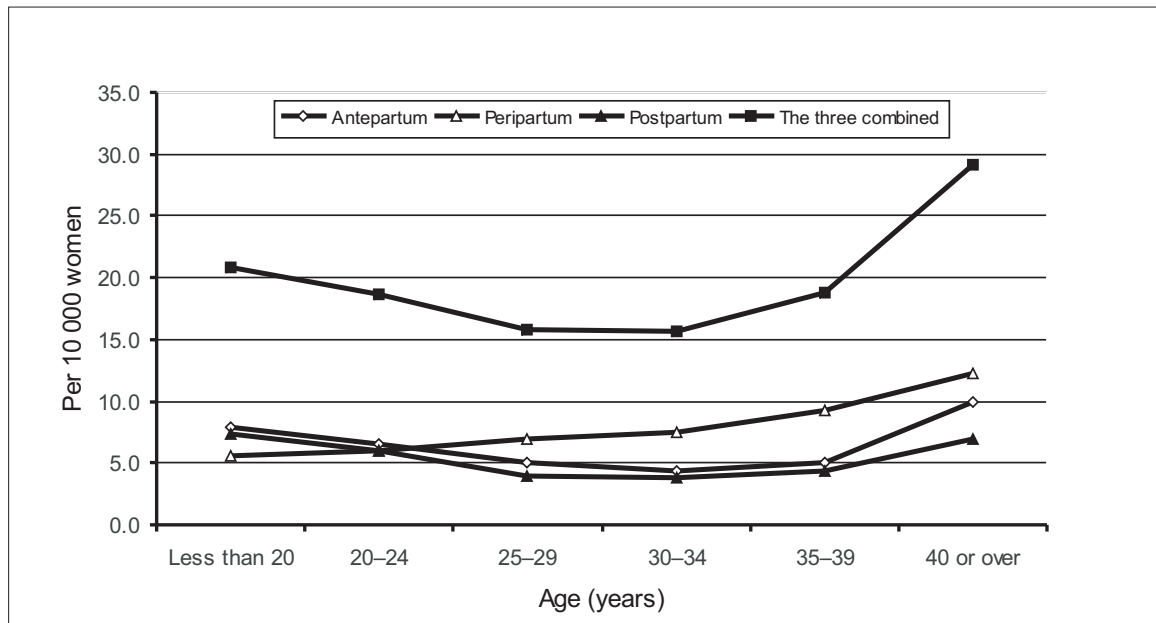
peripartum hospitalization included a previous DVT event in this pregnancy (aOR 56.9; 95% CI 40.9–79.1; aRD 271.8 per 10 000), heart disease (aOR 43.4; 95% CI 35.0–53.9; aRD 67.4 per 10 000), antiphospholipid syndrome (aOR 12.9; 95% CI 4.4–38.0; aRD 23.7 per 10 000), past history of circulatory disease (aOR 9.8; 95% CI 5.2–18.5; aRD 17.6 per 10 000), blood transfusion (aOR 4.5; 95% CI 3.3–6.2; aRD 6.3 per 10 000), major puerperal infection (aOR 4.1; 95% CI 3.0–5.6; aRD 15.8 per 10 000), systemic lupus erythematosus (aOR 3.9, 95% CI 1.9–7.8; aRD 5.8 per 10 000), Caesarean section (aOR 2.9; 95% CI 2.4–3.5; aRD 2.7 per 10 000), obesity (OR 2.7; 95% CI 1.6–4.4; aRD 16.7 per 10 000), thrombophilia (aOR 2.4; 95% CI 1.1–5.0; aRD 2.8 per 10 000), preterm labour (aOR 2.1; 95% CI 1.6–2.6; aRD 1.5 per 10 000), and anemia (aOR 1.7; 95% CI 1.3–2.2; aRD 1.2 per 10 000).

DISCUSSION

Our study showed a declining rate of pregnancy-associated deep vein thrombosis and a rising rate of pregnancy-associated pulmonary embolism in women hospitalized in Canada between 1991 and 2005. Among women hospitalized peripartum, DVT rates were stable (5.4 per 10 000 in 1991–1993 and 5.3 per 10 000 in 2003–2005), suggesting that the decline in pregnancy-related hospitalizations for DVT was probably due to a change in policy with regard to outpatient versus inpatient management of antepartum and postpartum DVT. The rate of death from VTE had declined sharply over the preceding decade, and our study identified various risk factors for DVT and PE.

Although a comparison with pregnancy-associated VTE rates derived from other reports is difficult because of differences in data collection and in the pregnancy and

Figure 3. Pregnancy-associated VTE occurrence (per 10 000 women) by maternal age during antepartum, peripartum, and postpartum periods, Canada (excluding Quebec and Manitoba), 1991 to 2005



postpartum period covered, our overall incidence rate is consistent with that reported in a study among Hong Kong Chinese women⁹ and in a study in the United States,¹² but is higher than other published studies.¹⁴⁻¹⁷ Chan et al. reported an incidence of VTE of 18.8 per 10 000 deliveries from 1998 to 2000, while James et al. reported 17.2 pregnancy-related cases of VTE per 10 000 deliveries,¹² based on data from the Nationwide Inpatient Sample in the United States in 2000-01; others have reported rates of pregnancy-associated VTE ranging from 7.1 to 12.5 per 10 000 deliveries.^{10,13,15,16,22,23} Differences in data sources and in the availability and utilization of various imaging or other diagnostic modalities may partially explain these variations. In addition, a population-based cohort study with careful case ascertainment conducted in Olmsted County, Minnesota, reported an overall VTE incidence during pregnancy and in the postpartum period (up to 3 months after delivery) of 199.7 per 100 000 woman-years, with a declining trend from 1966 to 1995.¹⁴

Postpartum VTE has been reported to be 3-5 times as frequent as antepartum VTE, and 3-16 times more common after Caesarean section than after vaginal delivery.^{14,21,22} Several studies,^{5,13,20,21} however, have reported that the antepartum period is the period of highest risk for DVT, while the immediate postpartum period after Caesarean section is the period of greatest risk for PE. As most DVTs are initially silent, and no more than one third show classic symptoms,^{13,34} we may have underestimated the true incidence of this disease, particularly in the early part of our

study period and during the antepartum period. Other potential differences include the restriction of our study to VTE among hospitalized women and our use of a cohort denominator that included all women at risk of VTE in each of the three periods. Because of changing diagnostic modalities used during the years of our study, the true incidence of DVT may have been underestimated or overestimated in the early study years when imaging techniques were less commonly used. Also, there has been a growing trend to manage cases of DVT on an outpatient basis.⁶⁻⁸ Our report of an increasing trend in PE is likely a consequence of improvements in diagnosis. In addition, changing practices related to the treatment of DVT, with a trend towards outpatient treatment, may have influenced the reported incidence of this condition in our data.

Although we observed a steady reduction in VTE-related mortality from the mid-1990s, the overall VTE mortality was 1.2 deaths per 100 000 pregnancies. This is consistent with the mortality rate from a recent study in the United States (1.1 per 100 000 pregnancies)¹² but lower than the 2 to 3 deaths per 100 000 women cited in previous reports,³⁵⁻³⁷ some of which included cases of amniotic fluid embolism. On the other hand, the case fatality rate for PE observed in our study (1.8%) was much lower than those cited in previous reports.³⁵⁻³⁷ However, we cannot explain the dramatic increase in mortality from VTE observed in the early 1990s.

Table 3. Rates of DVT, unadjusted and adjusted odds ratios by maternal characteristic, pregnancy complication, and obstetric condition

	Rate of DVT (per 10 000)		Odds ratio (95%CI)	
	Factor present	Factor absent	Unadjusted	Adjusted*
Maternal characteristic				
Maternal age \geq 35 years	6.9	5.1	1.3 (1.2–1.5)	1.2 (1.1–1.4)
Tobacco use disorder	6.9	5.4	1.3 (0.8–2.2)	1.0 (0.6–1.7)
Substance abuse	7.4	5.4	1.4 (0.8–2.3)	0.8 (0.4–1.5)
Obesity	14.0	5.4	2.6 (1.8–3.8)	1.8 (1.2–2.6)
Diabetes	8.0	5.3	1.5 (1.2–1.8)	1.1 (0.9–1.4)
Systemic lupus erythematosus	49.3	5.4	9.2 (5.1–16.6)	2.3 (1.1–4.8)
Sickle cell disease	18.9	5.4	3.5 (1.7–7.4)	1.3 (0.6–3.0)
Antiphospholipid syndrome	96.4	5.4	18.0 (6.7–48.2)	5.1 (1.8–14.3)
History of circulatory disease	98.4	5.4	18.5 (12.1–28.2)	8.0 (5.0–12.7)
Thrombophilia	145.9	5.3	27.9 (20.6–37.6)	15.4 (10.8–22.0)
Heart disease	31.7	5.3	5.9 (4.3–8.2)	3.2 (2.2–4.6)
Hypertension	9.1	5.2	1.7 (1.5–2.0)	1.1 (0.9–1.5)
Anemia	14.0	5.0	2.8 (2.4–3.2)	1.6 (1.4–1.9)
Pregnancy complication				
Multiple gestation	16.9	5.3	3.2 (2.5–4.0)	1.7 (1.3–2.2)
Thrombocytopenia	26.3	5.4	4.9 (2.2–10.9)	3.3 (1.5–7.5)
Hyperemesis	35.6	5.4	6.6 (3.7–12.0)	4.4 (2.4–8.4)
Disorders of fluid, electrolyte, and acid-base balance	65.6	5.4	12.2 (6.9–21.6)	1.6 (0.8–3.3)
Antepartum hemorrhage	14.4	5.2	2.8 (2.3–3.3)	1.6 (0.7–3.7)
Blood transfusion	55.0	5.2	10.6 (8.6–12.7)	3.6 (2.8–4.7)
Preeclampsia	8.6	5.3	1.6 (1.4–2.0)	0.8 (0.6–1.1)
Preterm labour	13.0	5.0	2.6 (2.3–3.0)	1.8 (1.6–2.1)
Prolonged pregnancy	5.6	3.3	0.6 (0.5–0.7)	0.5 (0.4–0.6)
Macrosomia	7.0	5.4	1.3 (1.0–1.7)	1.1 (0.9–1.5)
Fetal growth restriction	8.2	5.4	1.5 (1.2–2.0)	0.9 (0.7–1.2)
Obstetric condition				
Medical/surgical induction	8.8	4.8	1.8 (1.7–2.0)	2.0 (1.8–2.3)
Premature rupture of membranes	4.8	5.5	0.9 (0.7–1.0)	0.8 (0.6–0.9)
Fetal distress	6.6	5.3	1.3 (1.1–1.4)	1.1 (1.0–1.3)
Breech presentation	34.8	5.3	1.7 (1.4–2.0)	1.2 (1.0–1.4)
Dystocia	6.2	5.2	1.2 (1.1–1.3)	0.8 (0.8–0.9)
Placenta previa /abruptio	13.9	5.4	2.7 (2.2–3.2)	0.8 (0.3–1.8)
Polyhydramnios	12.5	5.4	2.3 (1.5–3.5)	1.4 (0.9–2.2)
Infection of amniotic cavity	13.3	5.3	2.5 (1.9–3.2)	1.4 (1.1–1.9)
Caesarean section	9.8	4.6	2.1 (1.9–2.3)	1.8 (1.6–2.0)
Postpartum hemorrhage	9.1	5.2	1.7 (1.5–2.0)	1.2 (1.0–1.4)
Major puerperal infection	53.9	5.1	10.6 (8.8–12.7)	6.1 (5.0–7.5)

*Adjusted by multiple logistic regression for all listed factors/conditions and also for year of birth, province of hospital delivery, elderly primigravida (first pregnancy at \geq 35 years of age) and grand multiparity (\geq 5 viable pregnancies).

Table 4. Rates of PE, unadjusted and adjusted odds ratios by maternal characteristic, pregnancy complication, and obstetric condition

Condition/factor	Rate of PE (per 10 000)		Odds ratio (95% CI)	
	Factor present	Factor absent	Unadjusted	Adjusted*
Maternal characteristics				
Maternal age \geq 35 years	2.6	1.9	1.4 (1.2–1.7)	1.0 (0.8–1.3)
Tobacco use disorder	3.0	2.0	1.5 (0.7–3.3)	1.5 (0.6–3.4)
Substance abuse	6.9	2.0	3.5 (2.1–6.0)	1.9 (1.0–3.7)
Obesity	11.6	1.9	6.0 (4.0–9.0)	2.7 (1.6–4.4)
Diabetes	4.2	1.9	2.2 (1.7–2.9)	1.4 (1.0–1.8)
Systemic lupus erythematosus	44.8	2.0	22.9 (12.3–42.8)	3.9 (1.9–7.8)
Sickle cell disease	13.5	2.0	6.8 (2.8–16.5)	1.4 (0.5–4.1)
Antiphospholipid syndrome	144.6	2.0	74.3 (33.1–166.8)	12.9 (4.4–38.0)
History of circulatory disease	58.2	2.0	29.9 (17.2–51.8)	9.8 (5.2–18.5)
Thrombophilia	43.1	2.0	22.1 (12.8–38.3)	2.4 (1.1–5.0)
Heart disease	128.4	1.6	80.8 (67.5–96.7)	43.4 (35.0–53.9)
Hypertension	6.1	1.7	3.5 (2.9–4.2)	1.2 (0.9–1.8)
Anemia	7.6	1.7	4.4 (3.6–5.3)	1.7 (1.3–2.2)
Pregnancy complication				
Multiple gestation	8.1	1.9	4.2 (3.0–5.9)	1.3 (0.9–1.9)
Deep vein thrombosis	325.5	1.8	185.1 (143.8–238.3)	56.9 (40.9–79.1)
Thrombocytopenia	4.4	2.0	2.2 (0.3–15.6)	0.6 (0.1–4.8)
Hyperemesis	9.7	2.0	5.0 (1.6–15.2)	2.2 (0.6–7.3)
Disorders of fluid, electrolyte, and acid-base balance	71.0	2.0	36.5 (21.1–63.3)	2.1 (1.1–4.3)
Antepartum hemorrhage	7.2	1.9	3.8 (3.0–5.0)	1.0 (0.3–4.4)
Blood transfusion	52.7	1.8	29.9 (24.0–37.3)	4.5 (3.3–6.2)
Preeclampsia	6.4	1.8	3.5 (2.8–4.4)	1.2 (0.8–1.8)
Preterm labour	7.3	1.7	4.3 (3.6–5.2)	2.1 (1.6–2.6)
Prolonged pregnancy	1.4	2.1	0.7 (0.5–0.9)	0.7 (0.5–1.0)
Macrosomia	3.5	2.0	1.8 (1.2–2.5)	1.5 (1.0–2.2)
Fetal growth restriction	4.8	1.9	2.5 (1.8–3.4)	1.4 (1.0–1.9)
Obstetric condition				
Medical/surgical induction	2.5	1.9	1.3 (1.2–1.8)	1.3 (1.0–1.6)
Premature rupture of membranes	1.7	2.0	0.9 (0.6–1.1)	0.7 (0.5–1.0)
Fetal distress	2.8	1.9	1.5 (1.2–1.8)	1.2 (1.0–1.5)
Breech presentation	4.2	1.9	2.2 (1.7–2.8)	1.2 (0.9–1.6)
Dystocia	2.5	1.8	1.4 (1.2–1.6)	0.8 (0.7–1.0)
Placenta previa /abruptio	7.1	1.9	3.8 (2.9–4.9)	1.3 (0.3–5.5)
Polyhydramnios	4.0	2.0	2.0 (1.0–4.2)	0.8 (0.3–2.0)
Infection of amniotic cavity	5.8	2.0	3.0 (2.0–4.5)	1.2 (0.8–1.9)
Caesarean section	5.0	1.4	3.5 (3.0–4.1)	2.9 (2.4–3.5)
Postpartum hemorrhage	4.9	1.8	2.6 (2.1–3.3)	1.3 (1.0–1.7)
Major puerperal infection	29.1	1.8	16.0 (12.4–20.5)	4.1 (3.0–5.6)

*Adjusted by multiple logistic regression for all listed factors/conditions and also for year of birth, province of hospital delivery, elderly primigravida (first pregnancy at \geq 35 year of age) and grand multipara (\geq 5 viable pregnancies).

Our univariate analysis showed that the risk of pregnancy-associated VTE during peripartum hospitalization increased with advancing maternal age. However, the crude effect of older maternal age on pregnancy-associated VTE was abolished in multiple logistic regression analyses. This can be explained by an increased prevalence of other strong risk factors, such as heart disease, obesity, and Caesarean section among older women.

Deciding who should receive thromboprophylaxis remains a challenge. It is generally recognized that all women should be assessed early in pregnancy for risk of VTE, and interventions such as early mobilization, hydration, compression stockings, and anticoagulation should be appropriately tailored to risk level. Knowledge of risk factors for VTE among pregnant and postpartum women is critical in identifying women who would benefit from prophylaxis.^{6-8,18,20} A history of circulatory disease and antiphospholipid syndrome appear to be important risk factors for VTE. Antecedents such as heart disease, thrombophilia, and prior DVT are strong risk factors for development of PE. Systemic lupus erythematosus, obesity, preterm labour, and Caesarean section are also important risk factors for women during peripartum hospitalization. We identified blood transfusion as a significant risk factor for pregnancy-related VTE, as was found in several previous studies.^{7,8,25} Although detailed information about the indication for blood transfusion was unavailable, conditions for which blood transfusion is typically required, such as anemia, antepartum hemorrhage, trauma, surgery (Caesarean section), and postpartum hemorrhage, also showed significant associations with pregnancy-associated VTE.^{12,24,25,28} Disorders of fluid and electrolytes and acid-base balance were associated with an increased risk of both PE and DVT. Major puerperal infection increased the risk of DVT and PE four- to six-fold, in parallel with findings from previous studies,^{11,12,17,20} and Caesarean section increased the risk of DVT and PE two-fold.

Our study has several limitations. First, our database did not include information on imaging and other diagnostic modalities. Thus, we cannot exclude potential errors in the diagnosis of DVT and PE, especially in the early years of the study. However, such diagnostic errors are likely to be non-differential with respect to some risk factors and thus should lead to conservative estimates of the association with VTE. For instance, underdiagnosis of DVT and PE is unlikely to have been different among women of different ages, and among women with and without diabetes. On the other hand, DVT and PE were probably overdiagnosed among those with well-known risk factors, especially in the early years of the study. However, logistic regression

analyses of risk factors with data restricted to five-year periods yielded essentially the same results.

Second, we used the number of hospital deliveries as the proxy for all pregnancies to calculate the incidence of VTE over the antepartum, peripartum, and postpartum periods. Cases of DVT and PE associated with early pregnancy losses would not have been captured by the database. Also it is important to note our definition of antepartum, peripartum, and postpartum VTE; the early postpartum period was included in the peripartum hospitalization, while postpartum hospitalizations referred to readmissions after discharge from hospital following childbirth. Third, there is no information in this database that indicates whether in-hospital deaths attributed to DVT or PE were confirmed pathologically or not. Nevertheless, our data in this study are consistent with earlier findings from the Canadian maternal mortality review, which obtained data from other sources.¹ Finally, we tested a number of risk factors in the multivariate logistic regression model. Although determinants were selected on clinical grounds and a priori knowledge regarding the pathophysiology of DVT and PE some type 1 errors (erroneous identification of risk factors) may have occurred.³⁸

CONCLUSION

There has been an increase over time in rates of pregnancy-associated pulmonary embolism in women hospitalized in Canada and a decline in mortality from pregnancy-associated venous thromboembolism between 1995 and 2005. Our study identified various risk factors for deep vein thrombosis and pulmonary embolism which could help clinicians to better identify pregnant women at risk for pulmonary embolism.

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