Venous thromboembolism in pregnant and puerperal women in Denmark 1995–2005

A national cohort study

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Summary

Venous thromboembolism (VTE) is the leading cause of maternal death in the Western world, and the risk increases during pregnancy and puerperal period. It was the objective of the present study to estimate the absolute and the relative risk of VTE at different weeks of gestation and in the postnatal period as compared to non-pregnant women. This was a historical controlled national cohort study. The National Registry of Patients identified relevant diagnoses. These data were linked to The National Registry of Medical Products Statistics for information about current use of oral contraceptives. Danish women 15 to 49 years old during the period January 1995 through December 2005 were included in the study. In total 819,751 pregnant women were identified of whom 727 had a diagnosis of VTE. The absolute risk of VTE per 10,000 pregnancy-years increased from 4.1 (95% CI, 3.2 to 5.2) during week 1–11 up to 59.0 (95% CI: 46.1 to 76.4) in week 40 and decreased in the puerperal period from 60.0 (95% CI:47.2–76.4) during the first week after birth to 2.1 (95% CI:1.1 to 4.2) during week 9–12 after birth. Compared with non-pregnant women, the incidence rate ratio rose from 1.5 (95% CI:1.1 to1.9) in week 1–11, to 21.0 (95%CI16.7 to 27.4) in week 40 and 21.5 (95% CI:16.8 to 27.6) in the first week after delivery, declining to 3.8 (95% CI:2.5 to 5.8) 5–6 weeks after delivery. In conclusion, the risk of VTE increases almost exponentially through pregnancy and reaches maximum just after delivery and is no longer significantly increased six weeks after delivery.

Keywords

Venous thromboembolism, pregnancy, pulmonary embolism, deep venous thrombosis

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Introduction

Venous thromboembolism (VTE) is still a leading cause of maternal death in the Western world (1). Pregnant women are known to have an increased risk of venous thrombosis. Venous stasis, hypercoagulability and tissue trauma are the physiological components of Virchow's triad increasing the risk of VTE in general. The increased risk of VTE early in pregnancy is caused by hypercoagulability due to the hormonal changes (2–4). Later in pregnancy venous stasis caused by the physical pressure of the growing uterus on the pelvic veins facilitates thrombosis. Late in pregnancy and during the puerperal period immobilisation increases the risk of VTE further. During labour and vaginal or abdominal birth, vascular damage occurs, further increasing the risk (5, 6).

Around 1 per 1,000 pregnancies is complicated by a VTE. The literature, however, is inconsistent concerning the magnitude of this risk according to gestational age (6–14). On this background we aimed to make a descriptive study estimating the absolute risk of VTE at different gestational ages in pregnant and puerperal women in Denmark. Furthermore, to estimate the relative risk of VTE they were compared to non-pregnant women not using hormonal contraception.

Material and methods

The study was designed as a historical controlled National cohort study, conducted by linkage between four National registries.

Data sources

The *National Registry of Patients* established in 1977 collects discharge diagnoses and surgical codes, classified according to World Health Organizations International Classification of Diseases (Version ICD-8 until end of 1993 and ICD-10 from 1994).

Statistics of Denmark includes updated information about length of schooling and any ongoing or completed education of Danish citizens.

The *Central Person Registry* includes a 10-digit personal identification number (PIN) of all Danish citizens given at birth or immigration, and daily updated information on actual address and vital status. The PIN is a unique personal identifier used in all public registries thus allowing reliable linkage between these registries.

The *National Registry of Medical Products Statistics* was established in 1994 being complete from 1995, records all redeemed prescriptions to all Danish citizens according to ATC codes and the amount of medicine prescribed in defined daily doses.

Study population

All Danish women 15–49 years old during the period January 1, 1995 through December 31, 2005 were identified in the Central Person Registry. When a woman turned 15 years she entered the study, and women were excluded at their 50th birthday. Emigrants were excluded at the moving date. The total study population then included 1,505,804 women. All pregnant women in the study population were identified in the National Registry of Patients. Women with a history before the study period of VTE, myocardial infarction, cerebral thrombosis and cancer, were excluded (n=3,463). Women using oral contraceptives, ovarian stimulation treatment or hormone therapy were identified in *The National Registry of Medical Products Statistics* and were censored from the control group while exposed.

Endpoint

Outcome for this study was VTE related to pregnancy. We included deep venous thrombosis of the lower extremities, pulmonary embolism, cerebral venous thrombosis, portal vein thrombosis, and amniotic- and air embolism (see Appendix).

From the National Registry of patients all non-pregnant women with VTE were identified from ICD-10: DI26, DI80.1, DI80.2, DI80.3, DI81, DI82.2, DI82.3, DI82.8 and DI82.9. Pregnant/puerperal women with VTE were additionally identified from ICD-10: DO08.7, DO08.7A-F, DO22, DO22.3, DO22.5, DO22.5A, DO22.8, DO22.9, DO87, DO87.1, DO87.1A, DO87.3, DO87.3A, DO87.8, DO87.9, DO88, DO88.0, DO88.0A, DO88.0B, DO88.1, DO88.1A, DO88.1B, DO88.2 and DO88.2A (Appendix). To identify women with previous VTE the corresponding ICD-8 codes from 1977 to 1995 were used: 450, 451.00, 451.08, 451.99, 452, 453.02, 631, 634.99, 671.01, 671.01, 671.08, 671.09 and 673.

Women with VTE were allocated according to the admission date and the diagnosis.

Confounders

Rate ratios were adjusted for maternal age, education and calendar year.

Educational level was categorised into four groups; 1: Elementary school and no ongoing or completed education, 2: High School and no completed education, 3: Any schooling and an ongoing or completed 3–4 years education, and 4: High school and ongoing or completed long education (5–6 years).

Statistical analysis

The absolute incidence rate and adjusted rate ratios of VTE among pregnant and puerperal women were calculated per 10,000 years with 95% confidence intervals (CI). The results were considered significant at p-values <0.05. To estimate the incidence rate ratio of VTE at different gestational age multivariate Poisson-regression analyses were made with control for age, calendar year and education. Test for interaction between age and pregnancy and education and pregnancy were made.

The study was approved by the Danish Data Protection Agency (J. no 2009–41–3483). Ethical approval is not required for registry-based studies in Denmark.

Results

The study population included 1,505,804 women, of whom 819,751 were pregnant at least once during the study period. In total 576,232 women were excluded. Among the 805,464 pregnancy outcomes, 120,851 were induced abortions, 83,850 miscarriages, 8,791 ectopic pregnancies, 656 hydatidiform mole and 591,316 deliveries, leaving 14,287 with ongoing pregnancy at the time of study closure.

During the 11-year study period, 727 women with VTE during pregnancy or puerperal period were identified. In pregnancy 12.4% of the VTE were diagnosed in first trimester, 15.3% in second trimester and 72.3% in third trimester. In the puerperal period, 74.5% of the VTE were diagnosed within the first four weeks after delivery.

Risk according to length of pregnancy

The risk of VTE in pregnant women was influenced primarily by the gestational age, and not by education or age (▶Table 1). There was no interaction between age and risk of VTE in various gestational ages.

The absolute risk of VTE per 10,000 pregnant women years rose from 4.1 (95% CI: 3.2 to 5.2) in week 1–11 up to 59.3 (95% CI: 46.1 to 76.4) in week 40. Puerperal women had an incidence rate of VTE

	Non-pregnant		Pregnant	
	VTE/ WY	IR (95% CI)	VTE/ WY	IR (95% CI)
Age				
15–19	79 / 827,356	1.0 (0.8–1.2)	12 / 11,577	10.4 (5.9–18.3)
20–24	152 / 622,863	2.4 (2.1–2.9)	65 / 67,951	9.6 (7.5–12.2)
25–29	298 / 889,932	3.4 (3.0–3.8)	185 / 172,126	10.8 (9.3–12.4)
30–34	392 / 1,225,052	3.2 (2.9–3.5)	161 / 147,666	10.9 (9.3–12.7)
35–39	505 / 1,468,824	3.4 (3.2–3.8)	60 / 52,684	11.4 (8.8–14.7)
40–44	707 / 1,573,804	4.5 (4.2–4.8)	7 / 8,088	8.7 (4.1–18.2)
45–49	839 / 1,548,251	5.4 (5.1–5.8)	1 / 373	26.8 (3.8–190.2)
Education				
Edu 1[a]	1272 / 2,366,661	5.4 (5.1–5.7)	109 / 96,969	11.2 (9.3–13.6)
Edu 2[b]	145 / 821,139	1.8 (1.5–2.1)	40 / 35,700	11.2 (8.2–15.3)
Edu 3[c]	984 / 2,803,864	3.5 (3.3–3.7)	196 / 182,886	10.7 (9.3–12.3)
Edu 4[d]	497 / 2,042,273	2.4 (2.2–2.7)	143 / 140,623	10.2 (8.6–12.0)

[a]Edu 1: Elementary school and no ongoing or completed education, [b]Edu 2: High School and no completed education, [c]Edu 3: Any schooling and an ongoing or completed middle education (3–4 years), [d]Edu 4: High school and ongoing or completed long education (5–6 years).

Table 1: Crude incidence rate (IR) of venous thromboembolism (VTE) per 10,000 women-years (WY) in pregnant and non-pregnant Danish women 15–49 years old according to maternal age and education.

Table 2: Incidence rate (IR) of venous thromboembolism (VTE) per 10,000 pregnancy-years (PY) according to gestational age (GA) and the week after delivery.

GA	VTE/PY	IR (95%CI)
Pregnancy		
1–11	61/149,893	4.1 (3.2 – 5.2)
12–23	75/130,998	5.7 (4.6 – 7.2)
24–27	53/43,541	12.2 (9.3 – 15.9)
28–31	68/43,489	15.6 (12.3 – 19.8)
32–35	75/43,111	17.4 (13.9 – 21.8)
36	12/10,579	11.3 (6.4 – 20.0)
37	24/10,356	23.2 (15.5 – 34.6)
38	30/9,838	30.5 (21.3 – 43.6)
39	33/8,548	38.6 (27.4 – 54.3)
40+	6010,111	59.3 (46.1 – 76.4)
Total	491/460,464	10.7
Puerperium		
1	66/10,992	60.0 (47.2 – 76.4)
2	53/10,969	48.3 (36.9 – 63.2)
3	40/10,939	36.6 (26.8 – 49.9)
4	17/10,903	15.6 (9.7 – 25.1)
5–6	23/21,582	10.7 (7.1 – 16.0)
7–8	11/21,159	5.2 (2.9 – 9.4)
9–12	8/37,982	2.1 (1.1 – 4.2)
Total	218/124,526	17.5

of 60.0 (95% CI: 47.2 to 76.4) in the week following delivery, and 48.3 (95% CI: 36.9 to 63.2) in week two after delivery decreasing to 2.1 (95% CI: 1.1 to 4.2) 9 to 12 weeks after deliveries (▶Table 2).

Pregnant women had a 1.5 times (95% CI: 1.1 to 1.9) increased relative risk of VTE in week 1–11 compared to non-pregnant women not using hormonal contraception. The relative risk increased through pregnancy up to 21 fold at term (95% CI: 16.7 to 27.4). The incidence rate ratio in the first week of the puerperal period fell from 21.5 (95% CI: 16.8 to 27.6), over 3.8 (95% CI: 2.5 to 5.8) in week 4–6 to 2 after puerperal week 6. From week 7 to 11 the incidence rate ratios were no longer significantly higher than among non-pregnant women (▶Fig. 1).

Discussion

The increased risk of VTE with an overall incidence rate at 10.7 per 10,000 pregnancy- years during pregnancy and 17.5 per 10,000 puerperal-years during the puerperium are in accordance with previous studies (7, 8, 14). The risk for VTE is strongly related to gestational age and reaches a maximum just after delivery.

Some previous studies reported the highest incidence rate of VTE ante partum (6, 9 –14) and some the highest risk just around time of delivery as in the present study (7, 8, 15). These different findings could be the results of different populations investigated, different designs and sizes of studies, diagnostic criteria and validity of data. Only few studies have investigated the incidence according gestational weeks (6, 7, 9, 15). Gherman et al. included 165 cases. In contrast to other studies, half of the ante partum events were diagnosed before 15 gestational weeks. They excluded events in women where anticoagulation therapy was initiated due to clini-

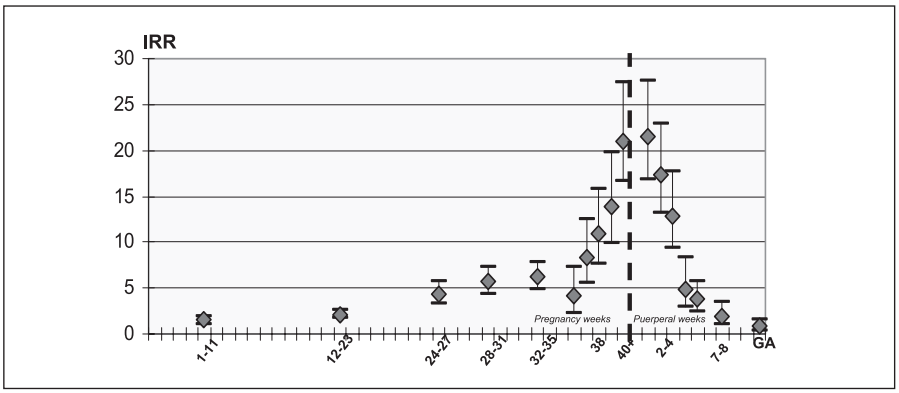

Figure 1: Adjusted* incidence rate ratios (IRR) of thromboembolism in pregnant and puerperal women versus non pregnant women not using oral contraceptives.
*Adjusted for age, calendar year and education.

cal suspicion, without describing the number excluded and at what specific gestational age. Potentially this could have excluded some of those having VTE post partum and therefore explain why their results differ from those of the present study (6). Another explanation of the difference in diagnoses of VTE in pregnancy versus the postnatal period in different studies could be that VTE diagnosed after delivery could be incomplete due to referral to other departments than to the obstetrical services as proposed by Greer et al. (16). In the present study we have tried to eliminate this potential bias by including diagnoses for both pregnant and non-pregnant women in the National Registry of Patients, which covers all departments.

In general, the risk of VTE increases with age and some studies have shown that age over 35 is a risk factor for pregnant women as well (11, 17). According to our data, however, this age effect was not apparent in pregnant Danish women. The recommended use of anticoagulation prophylaxis in older women may, however, have contributed to a reduction in VTE in these women. Also, the exclusion of women with previous VTE, previous cancer and previous cardiovascular diseases may have contributed to remove a crude age trend.

Limitations and strengths of the study

The validity of the registry data is of concern. In our study population 370 cases were coded with a specific pregnancy VTE code. The other 357 cases were found by combining a VTE-code for non-pregnant women with a register-based documentation of an ongoing pregnancy.

The diagnoses of VTE during pregnancy and the puerperal period in the National Registry of Patients have previously been evaluated by Larsen et al. (18). They investigated ICD-8 and ICD-10 codes of deep venous thromboses, pulmonary embolism or superficial thrombophlebitis in pregnancy or puerperal period from 1980 to 2001. They found an overall positive predictive value of VTE in pregnancy of 79.3%. There was a substantial variation in the positive predictive value of different codes. They did not find any differences in validity between ICD-8 and ICD-10 codes. The most common misclassification was between superficial thrombophlebitis and deep venous thrombosis (18). We did not include superficial thrombophlebitis, whereby our positive predictive value could be higher at expense of some lost events.

We also identified women with amniotic- and air embolism; however, only seven women were coded with these diagnoses.

White et al. reviewed ICD-9 codes for VTE in pregnant or puerperal women and found a positive predictive value for the pregnancy-specific codes of VTE of 30% and only detecting 36% of all VTE cases (19) Using both pregnancy and non-pregnancy codes for VTE, excluding 671.31, 671.42 and 671.9 in combination with the principal diagnosis only, the positive predictive value increased to 73%, detecting 67% of the VTE cases. ICD-9 codes in Denmark were never used.

The not complete validity could over- as well as underestimate the incidence of VTE in pregnancy and the puerperal period. Asymptomatic events of VTE will underestimate the incidence of VTE (6), and superficial events coded with a VTE code could overestimate the incidence rate.

Another limitation in the study is the precision of the date for first occurrence of disease. We defined the date of the VTE diagnosis as the date of admission. If VTE occurs before the patient is discharged after delivery, the date of admission could be several days before symptoms and diagnosis of VTE. Thus knowing the exact date of diagnosis would probably right-shift the curve. On the other hand, the first symptoms and a diagnosis of VTE may occur days or even weeks after the first thrombus formation.

What is known about this topic?

- Pregnant women have an increased risk of venous thromboembolism (VTE).
- Previous studies have shown conflicting results how this risk changes during pregnancy and the puerperal period.

What does this paper add?

- The risk of VTE reaches an up to 21 times higher risk just after delivery as compared to non-pregnant women.
- Seven weeks after delivery the risk is no longer significantly increased.

Appendix: ICD-8 and -10 codes used (black), also showing those excluded (gray).		
ICD-8	**ICD-10**	
VTE in non-pregnant women		
450	DI26	Pulmonary embolism
	DI80.1	Phlebitis and thrombophlebitis of femoral vein
451,08	DI80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
451	DI80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
452	DI81	Portal vein thrombosis
453,02	DI82.2	Embolism and thrombosis of vena cava
	DI82.3	Embolism and thrombosis of renal vein
451,99	DI82.8	Embolism and thrombosis of other specified veins
451,99	DI82.9	Embolism and thrombosis of unspecified vein
VTE in pregnancy or puerperium		
	DO08.2	Embolism following abortion and ectopic and molar pregnancy
631	DO08.7	Other venous complications following abortion and ectopic and molar pregnancy
	DO22	Venous complications in pregnancy
	DO22.0	Varicose veins of lower extremity in pregnancy
	DO22.1	Genital varices in pregnancy
	DO22.1A	Perineal varices in pregnancy
	DO22.1B	Vaginal varices in pregnancy
	DO22.1C	Vulval varices in pregnancy
	DO22.2	Superficial thrombophlebitis in pregnancy
	DO22.3	Deep phlebothrombosis in pregnancy
	DO224	Haemorrhoids in pregnancy
	DO22.5	Cerebral venous thrombosis in pregnancy
	DO22.5A	Cerebrovenous sinus thrombosis in pregnancy
634,99	DO22.8	Other venous complications in pregnancy
	DO22.9	Venous complication in pregnancy, unspecified
	DO87	Venous complications in the puerperium
	DO87.0	Superficial thrombophlebitis in the puerperium
671,01	DO87.1	Deep phlebothrombosis in the puerperium
	DO87.1A	Deep-vein thrombosis, postpartum
	DO87.2	Haemorrhoids in the puerperium
	DO87.3	Cerebral venous thrombosis in the puerperium
	DO87.3A	Cerebrovenous sinus thrombosis in the puerperium
671,08	DO87.8	Other venous complications in the puerperium
671,09	DO87.9	Venous complication in the puerperium, unspecified
	DO88	Obstetric embolism
673	DO88.0	Obstetric air embolism
	DO88.0A	Obstetric air embolism in the puerperium
	DO88.0B	Obstetric air embolism under partus
	DO88.1	Amniotic fluid embolism
	DO88.1A	Amniotic fluid embolism in the puerperium
	DO88.1B	Amniotic fluid embolism under partus
	DO88.2	Obstetric blood-clot embolism
	DO88.2A	Obstetric blood-clot embolism in the puerperium

Knowing the true date of the first thrombus formation would thus left-shift the curve.

Our data do have some strength compared to former studies mentioned above. Results are based on a national cohort of 819,751 consecutive pregnancies from 1995 to 2005. All women were followed through the pregnancy and puerperium. Also, the incidence rate ratios are relative to a control cohort of fertile, non-pregnant women, not exposed to exogenous oestrogen. In addition, potential recall bias and bias from non-responders were eliminated by our register approach.

Implications

Our findings, based on a National cohort with complete follow-up, suggest that anticoagulation therapy in pregnancy in women is in particular important during the third trimester and during the weeks after delivery.

Conclusion

The risk of VTE increases exponentially throughout pregnancy, from a four times increased risk to a 21 times increased risk at delivery. Puerperal women suffer from a 21 times increased risk just after delivery, decreasing to non-significant levels seven weeks after delivery. Maternal age was not a significant risk factor for VTE.

We need more knowledge about the interaction between gestational age and other acquired and genetic risk factors for VTE in order to expand our knowledge and understanding of VTE in pregnancy and puerperium.

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Conflict of interest

RAV, ECL, UM, JLR declare no support from any organisation for the submitted work. ØL has within the last three years received fees for speeches in pharmaco-epidemiological issues. TB has received fees for the institution by participating in an audit and expenses for congresses.

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