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Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database

E.L. Simpson*, R.A. Lawrenson, A.L. Nightingale, R.D.T. Farmer

Objective To determine the incidence of venous thromboembolism in pregnancy and the puerperium and to identify risk factors for pregnancy-related venous thromboembolism.

Design Cohort study and case–control study.

Setting London, UK.

Population 395,335 women with live births or pregnancies of 24 or more weeks of gestation between 1988 and 1997.

Methods Data extraction from the St Mary's Maternity Information System database. Random sample of 5% for case–control study.

Main outcome measures Incidence of venous thromboembolism; odds ratios for variables associated with venous thromboembolism.

Results The incidence of venous thromboembolism was 85/100,000 maternities. There were approximately twice as many postpartum as antepartum events. Blood group A, multiple pregnancy, caesarean section, cardiac disease, delivery at gestational age of <36 weeks, a body mass index of ≥ 25, or more and maternal age of 35 or over were all found to increase incidence of venous thromboembolism.

Conclusions Although venous thromboembolism is the leading cause of maternal deaths in the UK, it is still a rare event. Most of these events are deep vein thromboses occurring in the postpartum period. Antenatally multiple birth is an important risk factor. Postnatally women who have had a caesarean section, premature delivery or history of cardiac disease should be assessed carefully for venous thromboembolism.

INTRODUCTION

Virchow described a triad of initiating factors for venous thrombosis, namely hypercoagulability, venous stasis and vascular damage, all of which occur during pregnancy[1]. During pregnancy there are increased levels of most of the circulating clotting factors in preparation for placental separation[2]. Venous stasis in the lower limbs is caused by increased vein distensibility and the gravid uterus acting as a mechanical impediment to venous return[1]. Delivery can cause damage to pelvic vessels[3].

Pulmonary embolism is the leading cause of direct maternal deaths in the UK[4]. The incidence of venous thromboembolism during pregnancy and the puerperium has been estimated to be 5.5 – 6 times higher than in general female population of childbearing age[5,6]. A recent study in Denmark found the incidence rate of venous thromboembolism during pregnancy to be 85/100,000 maternities based on 54 cases[7]. Clinically confirmed deep vein thrombosis has been reported to be approximately 70/100,000 maternities in studies in Sweden, based on 11[8] and 17[9] cases, respectively, and in the UK, based on 51 cases[10]. A morbidity rate for pregnancy related pulmonary embolism of 15/100,000 maternities was calculated[10]. Peripartum incidence of intracranial venous thrombosis is lower at 8.9/100,000 maternities[11]. Venous thromboembolism events are estimated to be more common during postpartum than antepartum periods, by a multiple of approximately two[2] to three[1].

Risk factors identified for venous thromboembolism include age over 40, obesity, smoking, a blood group other than O, congenital and acquired thrombophilias, immobility, congestive heart failure, malignancy and hypertension. Pregnancy related risk factors include delivery by caesarean section[12], pre-eclampsia and eclampsia[13].

METHODS

The present study was conducted using the St Mary's Maternity Information System. The aim of this study was to calculate incidence rates of venous thromboembolism during pregnancy and the puerperium, and to identify risk factors for pregnancy-related venous thromboembolism.

The St Mary's Maternity Information System comprises data from maternity units in the former

Postgraduate Medical School, Guildford, Surrey, UK

* **Correspondence**: Dr E. L. Simpson, Postgraduate Medical School, Stirling House, Stirling Road, Surrey Research Park, Guildford, Surrey GU2 7DJ, UK.

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North Thames (West) region of the UK. This database records a range of information concerning pregnancies, including details of maternal medical histories. Information relating to complications during pregnancy is recorded with ICD codes at three stages: time of antenatal booking, delivery, and postnatally.

Ten years of data between 1988 and 1997 were available. Cases of venous thromboembolism were identified by searching the antenatal, delivery and puerperal complication fields using ICD9 (1988-1995) and ICD10 (1995-1997) codes (see Appendix 1). To calculate incidence rates we used a denominator of maternities which were defined as any pregnancy resulting in a live birth or stillbirth at or after 24 completed weeks of gestation[4]. Pregnancies not fulfilling these criteria were excluded from the study, as were any pregnancies that had incomplete records (usually due to the woman leaving the district prior to delivery).

Events were partitioned into antenatal and postnatal occurrence. We calculated the crude incidence rate of venous thromboembolism using maternities as the denominator. We also calculated age-specific incidence rates for maternal age at delivery and annual incidence rates of venous thromboembolism.

A case–control study was carried out to identify risk factors for venous thromboembolism in pregnancy. Variables thought to be relevant to pregnancy were abstracted from the database. We used an unmatched random 5% sample of women without a record of venous thromboembolism as controls. For the case–control analyses, data were partitioned into antenatal and postnatal events. Cases with both antenatal and postnatal events were included only in the antenatal analysis.

Forward and backward stepwise logistic regression analyses set to accept or remove variables at a significance of $P < 0.1$ were carried out. Variables entered into the models for both antenatal and postnatal events were: eclampsia: blood group status; Rhesus; body mass index at time of booking; number of infants this pregnancy; year event occurred; ethnicity; smoking status during pregnancy; epilepsy; history of hypertension; parity; diastolic blood pressure at time of booking; cardiac disease; renal disease; antepartum haemorrhage; maternal age at delivery; and diabetes.

In addition, the following variables were included in the models for postnatal data: method of delivery; gestation at delivery; feeding method at discharge. Unconditional logistic regressions were then performed using all the relevant variables identified by the stepwise logistic regression models to obtain adjusted odds ratios. Unadjusted odds ratios were also calculated for each variable.

Table 1. Annual incidence rates for venous thromboembolism in pregnancy.

Year	Cases	Maternities	Incidence/100,000 maternities (95% CI)
1988	27	37145	73 (45,100)
1989	40	39694	101 (70,132)
1990	43	41426	104 (73,135)
1991	37	41591	89 (60,118)
1992	34	41703	82 (54,109)
1993	29	41068	71 (45, 96)
1994	29	41715	70 (44, 95)
1995	22	36809	60 (35, 85)
1996	32	37323	86 (56,115)
1997	43	36861	117 (82,152)
All years	336	395335	85 (76,94)

RESULTS

Cohort analyses

There were 395,335 maternities with records of a completed pregnancy on the St Mary's Maternity Information System database for the period 1988–1997. Approximately 23% of the women were of non-European origin. Three hundred and thirty-six cases of venous thromboembolism were identified, giving a crude incidence rate of 85.0/100,000 maternities (Table 1). Antenatal cases comprised 82 deep vein thrombosis (ICD codes 671.3, O22.3, I80.2), 24 pulmonary embolism (ICD codes 415.1, I26) and three other venous thrombosis. Postnatal cases comprised 235 deep vein thrombosis (ICD codes 671.4, O87.1, I80.2), 18 pulmonary embolism (ICD codes 415.1, I26) and three other venous thrombosis.

The annual incidence rates ranged from 60/100,000 maternities in 1995 to 117/100,000 maternities in 1997. There was no significant difference between the rates for each year, and no trend over time. Incidence rates increased with increasing age (Table 2) (χ^2 for trend 4.91, $P = 0.03$). Age was not recorded for six maternities, and these were not included in the calculations for Table 2.

Between 1988 and 1997 there were 109 cases of antenatal venous thrombosis recorded giving an incidence rate of 28/100,000 maternities. The 256 cases of postnatal venous thromboembolism (including cases with both antenatal and postnatal events) gave a puerperal incidence rate of 65/100,000 maternities. In the antenatal cases the ratio of deep vein thrombosis to pulmonary embolism was 3.4:1, whereas in the postnatal cases the ratio was 13.1:1, demonstrating a higher incidence rate of

Table 2. Age-specific incidence rates (1988-1997).

Age group	Cases	Maternities	Incidence/100,000 maternities (95%CI)
<25 years	72	95,266	76 (58, 93)
25-34 years	207	250,534	83 (71, 94)
35>	57	49,529	115 (85,145)

Table 3. Unconditional logistic regressions for antenatal venous thromboembolism cases. Numbers in **bold** indicate statistical significance.

Characteristic	Unadjusted	Adjusted[a]
No. of infants delivered		
1	Reference	
≥ 2	**4.1 (1.8, 9.4)**	**4.2 (1.8, 9.7)**
BMI category		
<20	0.4 (0.2, 1.1)	0.4 (0.2, 1.1)
20-24.99	Reference	
25-29.99	1.2 (0.8, 2.0)	1.2 (0.8, 2.0)
≥30	1.4 (0.7, 2.5)	1.4 (0.7, 2.6)
Unknown	0.9 (0.5, 1.6)	1.0 (0.5, 1.7)
Blood group		
O	Reference	
A	**1.9 (1.2, 2.9)**	**1.9 (1.2, 3.0)**
B	1.5 (0.8, 2.8)	1.6 (0.9, 2.9)
AB	1.5 (0.6, 3.9)	1.6 (0.6, 4.1)
Unknown	1.5 (0.2, 10.8)	1.5 (0.2, 11.9)

[a] Adjusted for number of infants this delivery, BMI, blood group.

puerperal deep vein thrombosis than antenatal deep vein thrombosis.

The venous thromboembolism incidence rate following caesarean section was 178/100,000 (95%CI 143, 212) caesarean deliveries; approximately four times that following delivery by other methods. The cohort study also allowed investigation into the trends of smoking during pregnancy and percentage of deliveries performed by caesarean section. There was an increase in caesarean sections (from 12% to 18% of deliveries) and a decline in smoking (from 22% to 16% of maternities) between 1988 and 1997.

Case–control findings

The control group was a random 5% sample comprising 20,090 women. Antenatal cases were analysed separately from postnatal cases. For antenatal cases, the following variables were identified from stepwise logistic regression analyses: blood group A; two or more infants this delivery; body mass index of 25 or more. For postnatal events, as well as blood group A and body mass index of 25 or more, the following variables were significant: cardiac disease; gestational age at delivery; maternal age of 35 or more; caesarean section delivery; and artificial feeding at discharge.

A record of eclampsia was present in only 10 of the maternities, of which two had a venous thromboembolic event. Univariate analysis thus showed a strong association of eclampsia with venous thromboembolism, but with wide confidence intervals (antenatal 23.2 (2.9, 187.4); postnatal 29.4 (5.9, 146.5)). Eclampsia was not included in the multivariate analyses as it caused instability in the model.

We then calculated the adjusted odds ratios of venous thromboembolism using the variables identified from the stepwise analyses. These variables were then considered separately to obtain crude odds ratios. The crude and adjusted odds ratios for antenatal events and postnatal events are shown in Tables 3 and 4, respectively. Adjustment did not affect the odds ratios of the variables.

Blood group was unknown in less than 1% of maternities, as was gestation, whereas feeding method was not known for less than 5%. Nearly 20% of women on the database did not have sufficient data records from which body mass index could be calculated.

Multiple birth was significantly associated with antenatal venous thromboembolism. For both antenatal cases and postnatal cases, blood group A carried an increased risk of venous thromboembolism.

Postnatal venous thromboembolism was also significantly associated with cardiac disease, maternal age of 35 or more and body mass index of 25 or over. Women who delivered at a gestation of 36 weeks or less, who underwent caesarean section, or who used artificial feed-

Table 4. Unconditional logistic regressions for postnatal venous thromboembolism cases. Numbers in **bold** indicate statistical significance.

Characteristic	Sample A	
	Unadjusted	Adjusted[a]
Blood group		
O	Reference	
A	**1.5 (1.2, 2.1)**	**1.6 (1.2, 2.2)**
B	1.3 (0.9, 2.0)	1.4 (0.9, 2.1)
AB	1.3 (0.7, 2.6)	1.4 (0.7, 2.7)
Unknown	**3.2 (1.3, 8.0)**	2.6 (0.9, 7.0)
Gestation at delivery		
<36 weeks	**3.2 (2.3, 4.5)**	**2.4 (1.6, 3.5)**
37–41 weeks	Reference	
42 weeks and over	1.6 (0.8, 2.7)	1.5 (0.8, 2.6)
Cardiac disease		
No	Reference	
Yes	**5.1 (2.5, 10.5)**	**5.4 (2.6, 11.3)**
Maternal age at delivery		
<25 years	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)
25–34 years	Reference	
35 years and over	**1.5 (1.1, 2.2)**	1.4 (1.0, 2.0)
BMI at antenatal booking		
<20	1.3 (0.8, 2.1)	1.3 (0.8, 2.1)
20–24.99	Reference	
25–29.99	**1.8 (1.3, 2.5)**	**1.7 (1.2, 2.4)**
30 and over	**2.0 (1.3, 3.1)**	**1.7 (1.1, 2.6)**
Unknown	**1.5 (1.1, 2.2)**	1.3 (0.9, 1.9)
Method of delivery		
Spontaneous	Reference	
Caesarean section	**2.6 (1.9, 3.4)**	**2.0 (1.5, 2.7)**
Forceps	0.9 (0.5, 1.7)	0.9 (0.5, 1.6)
Ventouse	0.6 (0.3, 1.5)	0.6 (0.2, 1.5)
Breech	**2.8 (1.0, 7.7)**	2.2 (0.8, 5.9)
Feeding at discharge		
Breast	Reference	
Artificial	**1.5 (1.2, 2.0)**	**1.4 (1.0, 1.8)**
Supplemented	**1.8 (1.1, 3.1)**	1.5 (0.9, 2.6)
Unknown	**2.7 (1.4, 5.2)**	1.4 (0.7, 2.8)

[a] Adjusted for blood group; BMI; cardiac disease; gestation at delivery; maternal age; method of delivery; feeding method at discharge.

ing were also at increased risk of venous thromboembolism in the puerperium.

DISCUSSION

The crude incidence rate of venous thromboembolism in pregnancy or the puerperium was 85/100,000 maternities, similar to rates cited from other studies[6–9]. This indicates that if working in a unit with 5,000 deliveries per year, then four cases per year of pregnancy-related venous thromboembolism would be expected.

There were approximately twice as many postnatal as antenatal events identified, due to the increased rate of deep vein thrombosis postpartum rather than a difference in pulmonary embolism incidence rate. The nature of the database was such that postnatal data were collected during the period prior to discharge from hospital. Therefore postnatal events would be under-reported as those occurring after discharge from hospital would not be recorded. It has been estimated that 38% of puerperal deep vein thrombosis and 22% of puerperal pulmonary embolism manifest after discharge from hospital[3]. Specialist hospitals, to which women with cardiac problems would be referred, did not contribute and thus these women would be under-represented on the database. Given the association between cardiac disease and postpartum venous thromboembolism demonstrated in this study, it is reasonable to assume that the incidence rates of venous thromboembolism estimated here may be slightly lower than in the general UK pregnant population. We do not believe the high rate of venous thromboembolism postpartum is explained by any miscoding of cases of superficial thrombophlebitis, as the less specific ICD9 code 451.1 was not used.

The annual incidence for 1995 was low compared with other years. In 1995 there was a change over period from the use of ICD9 to ICD10 in this year we identified cases of venous thromboembolism from both ICD9 and ICD10, it is possible that this change over resulted in some coding problems leading to an underreporting of events.

Mortality rates were not investigated as the database, during the period studied, did not record cause of death. Based on mortality rates from the Department of Health [4] of 2.18/100,000 maternities, the expected number of deaths from thrombosis and thromboembolism on the database throughout the study period would be 8 or 9.

Women having multiple birth had a higher incidence of antenatal venous thromboembolism. Multiple birth has been linked with hypertension, antepartum haemorrhage, premature labour and surgical delivery[14]. Inclusion of these factors in the stepwise regressions still showed multiple birth as an independent risk factor.

Antenatal and postnatal venous thromboembolism incidence was increased in women with blood group A as compared with blood group O, which is consistent with previous findings[15] suggesting some genetic influence. There are conflicting reports on the influence of ethnic group on predisposition to venous thromboembolism. This study found no evidence of an association between ethnicity and pregnancy related venous thromboembolism, despite the large number of women in the study from ethnic minorities. Approximately 12% of this study population were from the Indian subcontinent. A review in 1985 found that pregnancy related venous thromboembolism was extremely rare in Africa and the Far East, and a low prevalence was found in Chinese women, which could have been related to the increase in protein level C at the end of pregnancy[6].

Increased risk of postpartum venous thromboembolism was significantly associated with the presence of cardiac disease. This is connected with the known risk factor of congestive heart failure [1]. As expected, maternal age of 35 and over was associated with increased risk of puerperal venous thromboembolism, as was a body mass index of 25 and over[13].

Method of delivery was a significant factor with caesarean sections being associated with an adjusted odds ratio of 2.0, compared with spontaneous vaginal delivery. Previous estimates have put the incidence of venous thromboembolism following caesarean section as being between 2.5[13] and 20[16] times that succeeding spontaneous vaginal deliveries, and this study found a four times increase in crude incidence. Artificial feeding at time of discharge carried greater risk of venous thromboembolism than breastfeeding.

The lack of significance of high diastolic blood pressure might have been due to the small number of women with a diastolic blood pressure of $\geq$90 mmHg ($<$2%). Hypertension was not found to be significant, but these records could have indicated history of the condition, or currently treated hypertension. Parity was not found to be a significant factor for venous thromboembolism risk in this study. However, this factor has previously been found not to contribute independently, but to correlate with increasing age[16].

Although the leading cause of maternal deaths in the UK, venous thromboembolism is a rare event. The majority of these events are deep vein thrombosis, most of which occur in the postpartum period. Increasing age is associated with increasing incidence of venous thromboembolism. Antenatally, multiple birth carries an increased risk of venous thromboembolism. Postnatally, women who have had a caesarean section, premature delivery or history of cardiac disease are also at increased risk and should be assessed carefully for venous thromboembolism.

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Appendix 1. International classification of diseases codes used to identify VTE events.

ICD9 codes (1988 – 1995)	
415.1	Pulmonary embolism
451.1	Phlebitis and thrombophlebitis of lower extremity
452	Portal vein thrombosis
453.2	Venous thrombosis and embolism of the vena cava
453.3	Venous thrombosis and embolism of the renal vein
325	Phlebitis and thrombophlebitis of intracranial venous sinuses
437.6	Nonpyogenic thrombosis of intracranial venous sinus
671.3	Deep phlebothrombosis, antepartum
671.4	Deep phlebothrombosis, postpartum
671.5	Other phlebitis and thrombosis (cerebral venous thrombosis) during pregnancy
673.2	Obstetrical blood clot embolism (puerperal pulmonary embolism NOS)
ICD10 codes (1995 – 1997)	
I26.9	Pulmonary embolism
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I81	Portal vein thrombosis
I82.2	Embolism and thrombosis of the vena cava
I82.3	Embolism and thrombosis of the renal vein
I63.6	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
I67.6	Non-pyogenic thrombosis of intracranial venous system
O87.1	Deep phlebothrombosis in the puerperium
O87.3	Cerebral venous thrombosis in the puerperium
O88.2	Obstetric blood clot embolism
O22.3	Deep phlebothrombosis in pregnancy
O22.5	Cerebral venous thrombosis in pregnancy

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