Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium—a register-based case-control study

Anne Flem Jacobsen, MD; Finn Egil Skjeldestad, MD, PhD; Per Morten Sandset, MD, PhD

OBJECTIVE: This study was undertaken to estimate the incidence of venous thromboembolism in pregnancy and puerperium and to identify risk factors for pregnancy-related venous thromboembolism.

STUDY DESIGN: A register-based case-control study with 613,232 pregnancies from 1990-2003 in 11 Norwegian counties. Medical records for eligible cases were revisited and relevant medical data were transferred to a specific case-report form. The diagnosis of venous thromboembolism was based on strict criteria. Data were analyzed by χ² test and forward stepwise logistic regression.

RESULTS: In total, 615 cases were detected. The incidence of venous thromboembolism was 1 per 1000 pregnancies. The ante- and postnatal incidences were quite similar. Antenatal risk factors were assisted reproduction, gestational diabetes, age older than 35 years, multiple pregnancies, and primi-parity. Postnatal risk factors were cesarean section, preeclampsia, assisted reproduction, abruptio placenta, and placenta previa.

CONCLUSION: We found different ante- and postnatal risk patterns. Assisted reproduction and gestational diabetes were significant antenatal risk factors; whereas cesarean section and preeclampsia were strong postnatal risk factors.

Key words: case-control study, pregnancy, risk factors, venous thromboembolism


Venous thromboembolism (VTE) is still one of the leading causes of maternal morbidity and death in the industrialized part of the world. Previous studies from Norway and the United States have found that the incidence of maternal mortality caused by VTE is approximately 0.48 per 100,000 and 1.1 per 100,000 deliveries, respectively.

Pregnancy induces a prothrombotic state with an increase in coagulation factors, a decrease in natural anticoagulants, e.g., the coagulation inhibitor protein S, and impairment of fibrinolysis, which is probably mediated by an increase in plasminogen activator inhibitor. These procoagulant changes are important to minimize blood loss during delivery. In pregnancy, all components of the Virchow’s triad occur during delivery (ie, hypercoagulability, venous stasis, and tissue damage). These homeostatic changes cause an increased risk of VTE.

Previous studies have found that the incidence of VTE varies from 0.6-2.0 per 1000 pregnancies. Some authors have reported a higher antenatal incidence, and others have found a higher postnatal incidence. Gherman et al identified the first trimester as the high-risk period, whereas McColl et al demonstrated the highest risk during the third trimester. Different study designs and validation of diagnosis may explain the wide range in observed incidences of VTE during pregnancy and puerperium.

Deep vein thrombosis (DVT) in the lower limb is the most common type of VTE, and during pregnancy, 70-90% of DVTs occur in the iliofemoral veins of the left leg. In a recent review, subclavian and jugular vein thrombosis were reported to be the most prevalent sites of thrombosis after hyperstimulation in women undergoing assisted reproduction.

Several pregnancy-related antenatal risk factors for VTE have been identified, including null parity, multiple pregnancies, and blood group A. Maternal age older than 35 years has been reported to be an antenatal risk factor in one study, but not in other studies. In the puerperium, most authors agree that high maternal age (>35 years) and operative delivery, preeclampsia, higher parity or order, heavy smoking, and blood transfusion are risk factors for VTE.

The purpose of this study was to estimate the incidence of VTE during preg-
nancy in a population-based setting focusing on ante- and postnatal differences.

**Materials and Methods**

From Jan. 1, 1990-Dec. 31, 2003, women with a diagnosis of VTE in pregnancy or postpartum in 18 hospitals in 11 of 19 Norwegian counties were identified through selected ICD-9 and -10 code search in the Norwegian Patient Register (Table 1 and Figure 1). In addition, ascertainment of case identification in the Norwegian Patient Register was validated for the entire study period by data on VTE in pregnancy at 3 major Norwegian hospitals (Ullevål University Hospital, Haukeland University Hospital, Bergen, and St. Olav’s Hospital, Trondheim) with data from the Medical Birth Registry of Norway. These 3 hospitals count for 32% of all deliveries in the current study.

**Case ascertainment**

Figure 1 shows the selection of cases from the Norwegian Patient Register. There were 1231 women registered with a diagnosis of VTE in 1396 pregnancies. After exclusion of possible cases with duplicate registration in one or more pregnancies, cases not fulfilling objective diagnostic criteria for VTE, cases that were incorrectly diagnosed with VTE in subsequent pregnancies after index pregnancy, and cases in which medical records were not retrievable, we identified 644 eligible cases. After inclusion of 2 cases that were identified through family members of participants, and exclusion of 3 more cases that gave birth outside the study period, and cases that had a diagnosis of VTE in association with spontaneous abortion, induced abortion, or ectopic pregnancy (n = 28) before completed gestational week 23, the final case population comprised 615 women.

**Control selection**

Data from the Medical Birth Registry of Norway revealed that 377,155 women, residents of the participating counties, gave birth to 626,762 newborn infants in 616,236 pregnancies during the study period. Because there were no cases among triplets and quadruplets, we excluded these pregnancies from the control group (234 triplets, 13 quadruplets). Furthermore, we excluded 13 pregnancies in which there were no valid data for year of birth of mother, and another 2744 pregnancies that were terminated before gestational week 23. After these exclusions, 613,232 pregnancies served as controls.

**Ascertainment of the diagnosis of VTE**

The diagnosis of DVT was objectively confirmed by compression or color Doppler ultrasonography or by venogra-

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**International classification of diseases codes related to VTE**

<table>
<thead>
<tr>
<th>ICD 8</th>
<th>ICD 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral vein thrombosis</td>
<td>325 Phlebitis and thrombophlebitis of intracranial venous sinuses</td>
</tr>
<tr>
<td>450 Pulmonary embolism</td>
<td>415.1 Pulmonary embolism</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>451 Venous thromboembolism</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>452 Portal vein thrombosis</td>
</tr>
<tr>
<td>Venous thrombosis in puerperium</td>
<td>453 Other vein thrombosis</td>
</tr>
<tr>
<td>673 Pulmonary embolism during pregnancy and puerperium</td>
<td>671.3, 4, 5, 9 Deep phlebothrombosis, antepartum, postpartum and other thrombosis during pregnancy</td>
</tr>
<tr>
<td></td>
<td>673.2, 3 Obstetric blood clot embolism, puerperal pulmonary</td>
</tr>
</tbody>
</table>

**ICD 10**

| G 08 Phlebitis and thrombophlebitis of intracranial venous sinuses |
| L 26 Pulmonary embolism                                           |
| L 80 Venous thromboembolism                                       |
| L 82 Other venous thrombosis                                      |
| O 22,3,5,8,9 Venous complications in pregnancy                   |
| O 87,1,3,9 Venous thromboembolism in puerperium                   |
| O 88,2 Pulmonary embolism in puerperium                          |

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**Flow chart**

phy. Pulmonary embolism (PE) was confirmed by perfusion lung scanning, computed tomography, magnetic resonance imaging, or angiography. For each procedure, diagnostic features were recorded. Patients who were treated on suspected, but not objectively confirmed criteria of diagnosis, were excluded (n = 56; Figure 1).

Data collection
Cases were identified at each participating hospital. The hospitals were asked to retrieve the medical records from the archives. One of the authors (A.F.J.) reviewed all medical records at the treating institutions. Relevant medical information was transformed to a specific case report form developed for the study.

Variable definition
Risk factors assessed were maternal age (<25, 25-29, 30-34, and >34 years), parity (0, 1, 2, and ≥3), assisted reproduction, multiple pregnancy, gestational diabetes, diabetes type 1, preeclampsia, eclampsia, premature rupture of membranes, abruptio placenta, placenta previa, delivery mode, and maternal mortality. By assisted reproduction, we included in vitro fertilization and intracytoplasmatic sperm injection.

Preeclampsia was defined as blood pressure 140/90 mm Hg or higher combined with albuminuria 0.3 g/L or more, whereas eclampsia was defined as preeclampsia with convulsions. Mode of delivery was categorized as vaginal delivery, vacuum extraction, forceps, and planned and emergency cesarean section.

Data processing and statistical analyses
All case report forms were scanned. Consistency analyses were run, and invalid data entries were corrected after a second review of invalid data in the appropriate medical records at the local hospital.

We defined pregnancy as a unit of analysis. Incidences were estimated as the number of events per 1000 deliveries with 95% confidence interval (CI). Risk factors were analyzed by χ² test and forward stepwise logistic regression, and presented as crude and adjusted odds ratios (OR) with 95% CI. Interaction between significant factors was tested at significance level P < .05. All data were analyzed by using the Statistical Package for Social Science version 13.1 (SPSS Inc, Chicago, IL).

Approvals
The study was approved by the Regional Committee for Research Ethics in Health Region East. Authorization for the use of data retrieved from medical records for research purposes was obtained from the Norwegian Ministry of Health and Social Affairs. The Norwegian Data Inspectorate approved the use of data comprising sensitive personal health information, merging of clinical data and register data by using the unique 11-digit personal identification number given to all Norwegian citizens.

RESULTS
We identified 615 cases with objectively confirmed VTE. Five hundred and ninety-five cases were identified in the Norwegian Patient Register, and another 20 patients were only identified in the Medical Birth Registry of Norway. The incidence of pregnancy-related VTE was 1.0 per 1000 pregnancies with no difference in antenatal and postnatal incidences (Table 2). DVT was more common antenatally than postnatally (0.43 vs 0.30 per 1000 deliveries, respectively), whereas PE displayed higher postnatal incidence (0.22 vs 0.06 per 1000 delivery.

![Figure 2](image)

**FIGURE 2** Distribution of VTE in pregnancy and puerperium

Number of VTE per week.

ies; Table 2). Women aged older than 35 years carried both a high ante- and postnatal incidence (0.66 and 0.66 per 1000 pregnancies).

The trimester distribution of VTE was 10.1% (n = 62) in the first trimester (weeks 3-12), 10.4% (n = 64) in the second (weeks 13-26), and 28.4% (n = 175) in the third trimester (weeks 27-42). Most VTEs (49.3%, n = 303) occurred during the first 6 weeks’ postpartum. The incidence then dropped rapidly and only 1.8% (n = 11) of all VTEs occurred during weeks 6-14 postpartum (Figure 2). There were 3 maternal deaths (0.48/100,000 deliveries), all postpartum.

Respectively, 301 and 314 cases were diagnosed ante- and postnatally. No case had both ante- and postnatal events. We identified different antenatal and postnatal risk profiles for VTE. Therefore, we analyzed the ante- and postnatal periods separately.

Maternal age, parity, assisted reproduction, multiple pregnancies, gestational diabetes, diabetes 1, preeclampsia, eclampsia, premature rupture of membranes, abruptio placenta, and placenta previa entered regression analysis. Antenatal age older than 35 years had a moderately increased risk, whereas gestational diabetes and assisted reproduction displayed higher risks (Table 3). The differences in unadjusted and adjusted ORs were fairly constant for all significant antenatal risk factors (age, parity, gestational diabetes, and premature rupture of membranes), except multiple pregnancies and assisted reproduction, in which adjusted ORs were considerably lower (Table 3). No interactions were found between the significant variables predicting antenatal VTE. Morbidity (diabetes type 1, preeclampsia, eclampsia) and delivery associated (abruptio placenta and placenta previa) risk factors were not significant for prediction of antenatal VTE. In 20, 9 VTEs after assisted reproduction were associated with ovarian hyperstimulation syndrome in the first trimester.

In addition to all variables entering the antenatal analysis, we included mode of delivery in the postnatal analysis. Forceps delivery and vacuum extraction did not differ from normal vaginal delivery in prediction of postnatal VTE, and were combined with vaginal delivery as the reference group. Although low parity order was associated with an increased antenatal risk, high parity order was associated with a significant postnatal risk. The postnatal risk factors are displayed in Table 4. There was

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Risk factors for antenatal VTE</th>
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<tbody>
<tr>
<td>Risk factor</td>
<td>Cases (n = 301) n (%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>13-24</td>
<td>51 (16.9)</td>
</tr>
<tr>
<td>25-29</td>
<td>97 (32.2)</td>
</tr>
<tr>
<td>30-34</td>
<td>95 (31.6)</td>
</tr>
<tr>
<td>35-54</td>
<td>58 (19.3)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>169 (56.1)</td>
</tr>
<tr>
<td>1</td>
<td>84 (27.9)</td>
</tr>
<tr>
<td>2</td>
<td>32 (10.6)</td>
</tr>
<tr>
<td>≥3</td>
<td>16 (5.3)</td>
</tr>
<tr>
<td>Premature rupture</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>No</td>
<td>298 (99.0)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>No</td>
<td>294 (97.7)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>No</td>
<td>281 (93.4)</td>
</tr>
<tr>
<td>Assisted reproduction</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>No</td>
<td>281 (93.4)</td>
</tr>
</tbody>
</table>

a large difference in unadjusted and adjusted ORs for all postnatal risk factors (preeclampsia, eclampsia, placenta previa, abruptio placenta, assisted reproduction, and planned and emergency cesarean section). Age, multiple pregnancy, and gestational diabetes did not predict postnatal VTE. Interaction terms were tested among all significant factors; however, no term was significant.

**Comment**

The crude incidence rate of VTE associated with pregnancy was 1.0 per 1000 deliveries. The incidences of ante- and postnatal VTE were similar, but the risk pattern differed. Antenatal risk factors seemed to be related to the woman’s constitutional conditions such as age, parity, numbers of fetuses, and way of conception, whereas postnatal risk factors seemed to be correlated to maternal morbidity and complications during and after delivery. The postnatal risk factors such as preeclampsia, eclampsia, and cesarean section has been published by others, but placenta previa has to our knowledge not previously been reported as a risk factor.

The population-based design and the retrospective validation of all diagnoses of VTE were strengths in this study. By primarily identifying cases in the Norwegian Patient Register validated against data collected by the Medical Birth Registry of Norway at 3 major hospitals, we found a small underestimation on antenatal VTEs in the range of 6-7% (20/301). Our total incidence was slightly higher than most studies with corresponding design, whereas Heit et al demonstrated a considerably higher incidence.

The weakness of the study might be inaccurate reporting of comorbidity to the Medical Birth Registry for variables such as preeclampsia and gestational diabetes. Our risk estimates for disease association rely on the incidence of disease in the control group, which corresponds to the completeness of reporting of maternal comorbidity to the Medical Birth Registry. If specific diseases are underreported to the Medical Birth Registry, biased results for disease association away from the null hypothesis will be estimated. As reported from another
country, we found a relatively high rate of invalid diagnosis of VTE in the Patient Register (Figure 1). Most women with an invalid diagnosis had wrong ICD-9 or -10 codes, or were referred with a suspected diagnosis of VTE, which was not confirmed during the hospital stay. Many patients had prophylactic treatment against VTE in pregnancy, and had VTE diagnosed accordingly. This might be caused by ignorance in coding praxis or to possible financial reasons. Norwegian hospitals are primarily financed by a diagnosis-related group system, and a diagnosis of acute VTE yields a higher reimbursement rate as compared with no history of VTE. According to these findings, we believe that incidence-studies on VTE in pregnancy that used national register data without validation of the diagnosis have certain limitations.

Most studies report overall risk for VTE during pregnancy and puerperium. Few authors have presented specific ante- and postnatal results. Our data conclude that ante- and postnatal risk patterns differed.

As reported by others we confirm that maternal age older than 35 years, null parity, and multiple pregnancies increase the risk of antenatal VTE in the magnitude of 1.6- to 2-fold. Our finding of gestational diabetes as an antenatal risk factor is consistent with only one previous study. But these investigators found an association with diabetes and not gestational diabetes. Our findings were not adjusted for weight gain during pregnancy or body mass index, because these data are not reported to the Medical Birth Registry. Furthermore, an underreporting of gestational diabetes in the Medical Birth Registry would bias our risk estimates of gestational diabetes away from the null hypothesis. The Medical Birth Registry of Norway reports an incidence on gestational diabetes of 0.5%, whereas Clausen et al reported an incidence of 1.2% in a recently published population-based prospective cohort study from Norway. Even with an incidence of gestational diabetes up to 1.2% in the control group, gestational diabetes would still be significantly associated with VTE.

Limited data are available on the magnitude of assisted reproduction as a risk factor. In our study, 9 of 20 antenatal VTEs after assisted reproduction were related to severe ovarian hyperstimulation syndrome. Interestingly, these thrombotic events were displayed as subclavian or jugular vein thrombosis during first trimester. We are only aware of 97 previously published thrombotic events associated with ovarian hyperstimulation syndrome. Severe ovarian hyperstimulation syndrome is reported in 0.56-6.5% of all hyperstimulations. This syndrome is associated with hemoconcentration and has very high levels of estradiol. Ascites is often present and sometimes pleural effusion. These clinical presentations combined with immobilization and pregnancy-induced hypercoagulability could make these women particularly predisposed for VTE. A possible underreporting of conceptions after in vitro fertilization to the Medical Birth Register would overestimate our risk association of assisted reproduction on the risk for VTE. However, annual hospital reports of women successfully treated with in vitro fertilization in Norway imply that the magnitude of this underreporting to the Medical Birth Registry would only have minor impact on our risk estimates.

As reported from Sweden, we have demonstrated that preeclampsia is a significant postnatal, but not antenatal risk factor. Our prevalence of preeclampsia was within the range of what is reported in another validated Norwegian study. Forty-four percent of our patients with preeclampsia and VTE delivered prematurely (<34 weeks) as did 13% of the controls. The early onset preeclampsia may have another pathophysiology and might be a more serious disease than late onset preeclampsia. In addition, the patients with early onset preeclampsia might have been immobilized over a longer period previous to delivery.

There was a tendency to higher incidence of VTE during the second compared with the first postnatal week (Figure 2). This tendency was even stronger in preeclamptic patients. Routine medical thromboprophylaxis administered 3-7 days after cesarean section probably prevents some events of VTE during the first postnatal week. In preeclamptic patients, a reactive thrombocytosis during 6-14 days after initial thrombocytopenia might be a contributing cause of disease.

As shown by others, we demonstrated a significant (P < .01) drop in the incidence of VTE 6 weeks postpartum (Figure 2).

Obstetricians are taught to counsel women about complications during pregnancy, but after delivery the women are transferred for follow-up in primary health care. Improved knowledge and more information to both patients and physicians about clinical signs and symptoms of VTE in pregnancy and puerperium may improve diagnostics and treatment of VTE.

In conclusion, we identified different ante- and postnatal risk patterns. Assisted reproduction and gestational diabetes were convincing antenatal risk factors. After delivery, we identified preeclampsia and cesarean section as expected, whereas placenta previa and assisted reproduction were risk factors that have not been previously published.

REFERENCES
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