

Postpartum thromboembolism: Severe events might be preventable using a new risk score model

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Background: Pregnancy-related venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. A new risk assessment model for VTE in relation to pregnancy has been introduced in Sweden. We wished to determine the proportion of preventable VTE cases if the model had been in use and make a brief cost-benefit analysis.

Methods: A hospital-based retrospective case-control study of all postpartum thromboembolic instances of deep venous thrombosis and pulmonary embolisms during a 16-year period. Large anamnestic risk factors at the time of delivery were assessed. We correlated the findings with the new Swedish guidelines for thromboprophylaxis.

Results: We found 37 cases of postpartum VTE during the study period. Nineteen of all VTE cases (51%) and eight out of eleven of cases of pulmonary embolism (73%) had two or more large anamnestic risk factors, ie, they would have been subjected to thromboprophylaxis if the new guidelines had been used. The cost of each preventable VTE was lower than treating a VTE.

Conclusion: Approximately one-half of postpartum VTE cases and 70% of pulmonary emboli cases have at least two large risk factors and might be preventable using the new algorithm. From the perspective of the health care system the new recommendations appears to be cost-effective.

Keywords: thromboprophylaxis, low molecular weight heparin, scoring system, health care financing, ultrasonography, phlebography

Introduction

Pregnancy-related venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality in Western countries (Drife 2003). Normal pregnancy is associated with a manifest shift of the coagulation and fibrinolytic systems towards hypercoagulability. Although these changes are of physiological importance in minimizing the risk of blood loss during delivery, they also increase the risk of thromboembolism. Some major predisposing factors are increasing maternal age, operative delivery, immobilization, obesity, heart disease, malignancy, Caucasian descent, a history of thrombosis, thrombophilia, and familial thrombosis.

The incidence of VTE is reported to be about 13/10,000 pregnancies, about half occurring before delivery and the other half in the puerperal period (Lindqvist et al 1999). Thus, during a six-week span, the risk of VTE increases roughly 5-fold as compared to the antepartum period. In addition, it has been shown that the puerperal risk of thromboembolism is highest in the immediate postpartum period (Salonen Ros et al 2001). Furthermore, preeclampsia and caesarean section only have an impact on thrombosis risk during the puerperal period (Lindqvist et al 1999). Therefore, a higher risk level is present over a shorter time span with the risk decreasing in time. Based on this knowledge, the Swedish medical establishment has implemented a risk score

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model (presented below) for estimating the likelihood of pregnancy-related VTE. Factors having a 5-fold increased risk or multiples thereof are included. The model recommends to whom, when, at what dose, and for how long thrombosis prophylaxis is recommended for pregnant women. Guidelines on the use of thromboprophylaxis have reduced deaths after cesarean delivery (Drife 2003).

The following study was conducted in the area of Malmö, Sweden, in an attempt to assess the number of risk factors among women who developed a VTE during the postpartum period. We also present the national risk assessment model for VTE in relation to pregnancy and estimate the proportion of preventable cases, if the algorithm had been used during the study period. A brief cost-benefit analysis is also included.

Methods

All women with VTE during the first six weeks after delivery at Malmö University Hospital, MAS, between 1990 and 2005 were identified out of a total of 51,968 deliveries. There is one radiological clinic serving the entire Malmö area. By using national personal identification numbers, all pregnant women during the study period were cross-matched against the diagnostic procedures they received, allowing the major proportion of VTE cases to be identified. We also searched the diagnosis numbers for thromboembolic complications at the hospital during the first six postpartum weeks. Only direct signs of VTE were included, ie, contrast filling defects. Indirect signs of deep venous thrombosis (DVT) were not accepted. One woman had a diagnosis of DVT, but on our special interpretation, we found no direct signs of the thrombosis and she was excluded. As previously described in detail, we took all women who delivered ($n = 2,384$) in the prospective unselected pregnant cohort as a reference group (Lindqvist et al 1999). In brief, 2,480 unselected pregnant women were recruited in early pregnancy for detailed anamnesis and blood sampling. They were followed without intervention, but special attention was paid to thromboembolic and bleeding complications. Not earlier than three months postpartum, the blood samples were analyzed. Previously, we have reported on the distribution of risk factors in this population (Lindqvist et al 2002b).

We defined VTE as a deep venous thrombosis or pulmonary embolism occurring during the first six weeks postpartum. The phlebograms, computerized tomographies (CT), and ultrasonographies were interpreted by two radiologists. In Malmö, at the present time, our preference is to use CT before ventilation/perfusion scintigraphy in diagnosing

pulmonary embolism in order to lower the radiation dose to the fetus (0.05 mSi versus 2 mSi, as estimated by our radiophysics department).

Preeclampsia was defined as pregnancy-induced hypertension and proteinuria >0.3 g/1 (Albuminuria dipstick $\geq 1+$). Pregnancy-induced hypertension was defined as a resting diastolic blood pressure >90 mm Hg measured on two occasions separated by an interval of at least five hours, and developing after 20 weeks of gestation in a previously normotensive gravida.

We considered abruptio placenta as the diagnosis of such, commonly based on the presence of uterine pain and vaginal bleeding in combination with the finding of blood clots behind the placenta.

Overweight was defined as a maternal body mass index (BMI) measured at the first visit to the antenatal health clinic of BMI (kg/m^2) ≥ 28 , which is one standard deviation (SD) above the mean of our pregnant population (Lindqvist et al 1999).

A heredity of thrombosis was defined as one or more thromboses in first-degree relatives (father, mother, or siblings) occurring before the age of 60. Immobilization was defined as strict bed rest for more than one week.

The price of low molecular weight heparin (LMWH) used in our financial analysis was the price paid by the hospital.

The Swedish risk assessment guidelines for VTE and thromboprophylaxis in relation to pregnancy is presented in Table 1. Risk factors included in the guideline and the weight they were given are shown in Table 1. Clinical recommendations as to whom, when, at what dose, and for how long thromboprophylaxis is recommended at different scores is presented in Table 2. The basis of the risk estimates have previously been published (Lindqvist et al 1999a, 1999b; Lindqvist et al 2002b).

Statistics

The odds ratio (OR) for the risk of VTE was calculated by cross-tabulation with a 95% confidence interval (CI). Relative risk was determined in terms of ORs (95% CI). All calculations were performed with SPSS software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) and p values <0.05 were considered statistically significant.

Results

The number of VTEs over the 16 years we studied totaled 37, representing an incidence of puerperal VTE of 7.1/10,000. In Table 3 we present risk factors present among women with

Table 1 Riskscore – risk factors and their weight

1p (ie, 5-fold increased risk)	Heterozygous FV Leiden
	Heterozygous protrombin gene mutation
	Overweight (>28 in BMI in early pregnancy)
	Cesarean section
	Familial thrombosis less than 60 years
	Maternal age >40 years
	Preeclampsia
	Abruptio placenta
	Other large risk factor
2p (ie, 25-fold increased risk)	Protein S-deficiency
	Protein C-deficiency
	Immobilization (ie, plaster-treatment, strict bed rest \geq 1 week, or over-stimulation syndrome) ¹
	Lupus antikoagulans ²
	Cardiolipin antibodies ²
3p (ie, 125-fold increased risk)	Homozygous FV Leiden
	Homozygous prothrombin gene mutation
\geq 4p High risk (10% absolute risk of VTE in relation to pregnancy)	Prior venous thromboembolic event (VTE)
	Antiphospholipid syndrome (APS) without prior VTE ²
Very high risk (>15% absolute risk of VTE) ³	Mechanical heart valves
	Continuous warfarin prophylaxis
	Antithrombin deficiency
	Repeated thromboses
	APS with prior VTE ²

¹At immobilization during pregnant short term thromboprophylaxis is recommended, ie, during the risk period.

²Women with APS, lupus anticoagulants, or anticardiolipin antibodies are also recommended low-dose ASA 75mg /d.

³Women with "very high risk" are recommended high dose prophylaxis (ie, twice daily with anti factor X activity remaining before next injection).

postpartum VTE and our reference group. All VTEs were verified by objective methods: ultrasound (n = 14), intravenous phlebography (n = 25), CT (n = 8), and ventilation/perfusion scintigraphy (n = 2), or pulmonalis angiography (n = 2). Some women were examined by more than one method.

Table 4 shows the main outcome of this study, ie, the distribution of risk scores in the reference group as compared with the VTE group and to the subgroup of cases with pulmonary embolisms. Fifty-one percent (19/37) of the postnatal VTEs and 73% (8/11) of the cases with pulmonary embolisms had two or more anamnestic large risk factors. Of the three women with pulmonary embolisms and a low risk score (0 or 1), one had a protein S deficiency, one a protein C deficiency, and one an antithrombin deficiency. The final six years (2000–2005) showed a lower incidence of postpartum VTE (9/21,702 or 4.1/10,000) as compared to the ten previous years (1990–1999) (28/30,265 or 9.3/10,000), OR = 0.45, 95% CI 0.2–0.95 as compared to the first period.

Two women were stricken with puerperal VTE despite thromboprophylaxis. The first had had two prior VTEs and protein S deficiency. She was treated with normal dosage prophylaxis, although according to the algorithm she should have received high dosage; she suffered a VTE five days after delivery. The second woman, who had had one prior VTE as well as a protein S deficiency, had a rethrombosis five days after delivery. She experienced painful bruising from the LMWH and was switched to warfarin after delivery. The LMWH was continued for three days according to standard practice at the time.

Table 5 presents a rough estimation of the cost of thromboprophylaxis as per the established routine in Sweden for women with a history of VTE (risk score 4). For these women prophylaxis is recommended from early second trimester until six weeks after delivery. Also estimated is the cost associated with the new algorithm. The data shows the cost-effectiveness of prophylactically treating women whose risk score is two or three. Finally, we have approximated the potential number of VTE cases that are preventable employing both methods and have calculated the cost of preventing one VTE. If the cut-off level had been set at risk score 1, some 24% more of the VTEs would have been preventable. However, the direct cost per additional preventable case would have been considerable higher than treating the complication, ie, \$13,051 (2,200 \times 10/7 times 0.243).

Discussion

In this paper we report that about one-half of the puerperal VTEs and two-thirds of the subgroup with postpartum pulmonary embolism were at an anamnestic risk score of at least two points, ie, these events might have been prevented if the new algorithm had been in use. In addition, the risk level of more

Table 2 Management based on risk score (the sum of risk points in Table 1)

Risk score 0	No treatment
Risk score 1	No treatment
Risk score 2	Short term (7 days) LMH prophylaxis after delivery or during immobilization
Risk score 3	6 weeks of LWH prophylaxis after delivery*
Risk score \geq 4	Antepartum prophylaxis, and at least 6 weeks postpartum**
"Very high risk"	High dose antepartum prophylaxis and at least 12 weeks of puerperal prophylaxis***

*Initiated 4 hours after delivery.

**Women with anamnesis of VTE initiate the antepartum prophylaxis during second trimester.

***Prophylaxis is initiated as early as possible and sometimes before pregnancy.

Table 3 Risk factors for VTE in study and reference groups

	Postpartum VTE group		Control group		Odds ratio	
	(n = 37)	%	(n = 2384)	%		95% CI
Maternal characteristics						
Maternal age (years)						
≤40	36	97.3%	2340			
>40	1	2.7%	26	1.1%	2.5	(0.3–18.9)
Preeclampsia						
No	31	83.8%	2345			
Yes	6	16.2%	39	1.6%	11.6	(4.6–29.5)
Cesarean section						
No	22	59.5%	2314			
Yes	15	40.5%	233	9.8%	6.8	(3.4–13.2)
Familial thrombosis (first degree relatives <60 years)						
No	31	83.8%	2257			
Yes	5	13.5%	127	5.3%	2.9	(1.1–7.5)
missing	1					
Anamnesis of venous thromboembolism						
No	35	94.6%	2376			
Yes	2	5.4%	8	0.3%	17.0	(3.5–83)
Body mass index (Kg/m ²)						
<28	26	70.3%	2067			
≥28	9	24.3%	317	13.3%	2.3	(1.05–4.8)
Missing	2					
Immobilization						
No	26	70.3%	na			
Yes	10	27.0%	na		na	
Missing	1					
Abruptio placenta						
No	33	89.2%	2371			
Yes	3	8.1%	13	0.5%	16.6	(4.5–61)
Missing	1					

than 70% of the subgroup with pulmonary emboli would have warranted LMWH prophylaxis according to the new algorithm. Recalling that approximately two-thirds of lethal VTEs occur in the postnatal period, approximately one-half of the severe postnatal cases might have been preventable.

It should be noted that the model makes provision for “other large risk factors”. This will permit clinicians to insert factors not included in the model, enabling them to add an extra point or points to the risk score based on their judgment in such cases as, women with a severe family history of thromboembolism, women with cancer, women who have been treated for cancer, or extremely obese women.

To the best of our knowledge there are no reports of the risk reduction afforded by thromboprophylaxis in obstetric patients. Approximately 71% to 75% risk reduction is

reported after general surgery (Mismetti et al 2001). Since pregnant women are generally younger, healthier, and have less co-morbidity than the general population of VTE among women, the relative risk reduction is presumably higher.

The model does not account for the 30% increased risk among smokers or for differences occasioned by parity (Lindqvist et al 1999). Before the present risk score model was accepted for national implementation, an internet-based alternative was also proposed, which took these differences into consideration and gave an estimation of the absolute risk of VTE (Lindqvist et al 2002a).

Friedrich and colleagues (1996) found women with protein S deficiencies to be especially prone to postpartum VTE. Both women who experienced VTE despite thromboprophylaxis, exhibited a protein S deficiency and

Table 4 Distribution of risk score in reference and study groups

	Reference group		Postpartum VTE group		Postpartum pulmonary emboli	
	(n = 2384)	(%)	(n = 37)	(%)	(n = 11)	(%)
Risk score*						
Risk score 0	1758	74%	10	27.0%	2	18.2%
Risk score 1	515	22%	9	24.3%	1	9.1%
Risk score 2	96	4.0%	10	27.0%	4	36.4%
Risk score 3	7	0.3%	3	8.1%	2	18.2%
Risk score ≥ 4	8	0.3%	5	13.5%	1	9.1%

*Risk score based on anamnestic variables present at delivery.

early postnatal VTE (one at risk score 4 and one at very high risk). There may be indication for high dosage prophylaxis in the immediate postnatal period among women with protein C or protein S deficiencies, due to the initial depression of protein S and protein C levels. Therefore, the current routine for women with protein S or protein C deficiency if one switches to warfarin postpartum is to accompany the warfarin treatment with LMWH for one week.

Not all variables in the risk table have been shown to have a roughly 5-fold increased risk.

Maternal age >35 is an established risk factor (Drife 2004), although the heightened risk has been related to an increased

rate of cesarean sections with age (Lindqvist et al 1999). It was considered essential to include high age as a large risk factor. Around 10% of our pregnant population is above 35 years of age, but only some 1.1% of all women are above 40. The risk of VTE grows with increasing age. For this reason age >40 was included in our model. Some changes were made to conform clinical practice. Homozygous factor V Leiden (FVL) represents 16- to 80-fold increased risk of VTE (Martinelli et al 2001; Juul et al 2004), but this factor was allotted 3 points (ie, a 125-fold increase). Women with homozygous FVL always receive six weeks of postpartum prophylaxis and, if they have additional large risk factors, antenatal prophylaxis

Table 5 Estimated cost for thromboprophylaxis of both established and according to new algorithm

	Established routine	New routine	
	Prophylaxis to women with prior VTE	Risk score 3	Risk score 2
Time of prophylaxis/women	30 weeks ¹	6 Weeks	1 Week
Cost per week	\$10	\$10	\$10
Incidence in pregnant population ²	0.3%	0.3%	4%
Number of women per 10,000 ²	30	30	400
Estimation of cost in population per 10,000 ³	30*\$10*30 \$9000	30*\$10*6 \$1800	400*\$10*1 \$4000
Cost per 10,000 women	= \$9000		\$5800
Expected no of VTE	10%		7/10,000 ⁴
Possible preventable VTE cases per 10,000 pregnancies ⁶	3		3.4 ⁵
Cost per preventable VTE case	\$3000		\$1700
Cost per patient (CPP) price for VTE ⁷			
Deep venous thrombosis	\$5580		
Pulmonary emboli	\$7836		

¹Some 24 weeks during pregnancy and 6 weeks after delivery.

²According to our prior data (Lindqvist et al 2002b).

³Only including cost of LMWH, about \$10/week.

⁴Data from this and prior study (Lindqvist et al 1999).

⁵Data from this study about 50% preventable.

⁶Possible preventable cases assuming 100% riskreduction.

⁷According to Swedish National Board of Health (Socialstyrelsen) 2006.

is also given. Due to the infrequent occurrence of these rare variables, their adjustment will not have a great effect on the discriminative potential of the model.

Approximately half of all VTE occur among women with risk score 0 or 1 and are not preventable by the present risk model. By changing the risk level of prophylaxis to risk score 1, some 25% to 40% more pregnant women (depending on the number of cesarean deliveries) would be treated, resulting in another 25% of the VTEs being possible to prevent. However, at this lower risk level a careful analysis of increased bleeding complications is needed, especially if the prophylaxis is initiated antepartum. Women with antepartum thrombosis prophylaxis have a 4-fold increased risk of profuse hemorrhage during delivery and a 6-fold increased risk of postpartum anemia (Lindqvist and Dahlbäck 2000). Therefore, it is our practice to initiate all thromboprophylaxis four hours after delivery in order to keep bleeding complications low.

The current paper includes only risk factors that could be ascertained by anamnesis. Since the introduction of this risk model (Lindqvist et al 2006), abruptio placentae has been added as a significant risk factor (Preston et al 1996; Prochazka et al 2003, 2007).

For 50 years, the Royal College of Obstetricians and Gynecologists (RCOG) have collected data on lethal thromboembolism as a result of their confidential enquiries into maternal deaths (Drife 2004). Prevention of VTE has been a major issue in their attempt to lower maternal mortality. Their model, although similar to ours, differs in several ways, the main difference being that the RCOG includes all risk factors, while we consider only large ones. Increasing age is a risk factor, but not a discriminative one. In the English model, preeclampsia is regarded as a risk factor both ante- and postpartum, whereas we only take it into account postpartum (Lindqvist et al 1999). We have concluded that the increased risk for multiparity is too small to be included in our model, but it is included by the RCOG (Lindqvist et al 1999). In addition, the British model includes several risk factors for which we believe insufficient data on the size of risk is available at present. However, several of these factors are candidates for future inclusion in our model. The British model also recommends short-term postnatal prophylaxis for three to five days. If this should prove effective, it will facilitate the clinical management of women at increased risk. In Sweden, we still believe that at least seven days of prophylaxis is needed postpartum.

Although it was not a predetermined analysis, the finding of a lower thrombosis incidence during the second time period

(2000–2005) might be attributed to the use of the algorithm in lowering the postpartum incidence of thrombosis. A local awareness of an increased risk among women with multiple large risk factors caused clinicians at our hospital to begin using the model before it was officially introduced in 2005.

Economic factors

There was an almost a 4-fold lower direct cost of LMWH as compared to the cost of treating VTEs. In addition, postnatal thromboprophylaxis has the potential of cutting in half the incidence of pregnancy-related pulmonary embolism, thereby lowering maternal mortality by one-twelfth (assuming that about one-sixth of maternal deaths are due to pulmonary embolism) (Drife 2003). Furthermore, we have not taken into consideration long-term morbidity, negative impact on quality of life among VTE patients (Kahn et al 2002), or to other indirect costs. The new recommendations for postpartum prophylaxis involve no additional expense other than LMWH, ie, no additional visits or laboratory tests. However, women with a history of VTE (risk score 4) are usually scheduled for two visits to the physician, one at the beginning of the second trimester and one in the 34th week. In addition, prothrombin time, APTT, and platelet count is performed in second trimester and during delivery, and platelets are also measured two weeks after initiation of thromboprophylaxis. Thus, prophylactic postpartum treatment according to the new algorithm appears to be very favourable for the health care system, especially when compared to the cost of treating cases of deep venous thrombosis and pulmonary embolism.

Our findings indicate that about half of puerperal VTE cases and two-thirds of pulmonary emboli cases have at least two large risk factors (ie, risk score 2). Thus, employing the risk score model presented here, approximately half of all severe VTE cases might be preventable.

Disclosure

The authors report no conflicts of interest in this work.

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