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ORIGINAL ARTICLE

# Individual risk assessment of thrombosis in pregnancy

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*Background.* Thromboembolic complications during pregnancy are major contributors to maternal death, but there is no reliable way to estimate the absolute risk of thrombosis before the occurrence of a thromboembolic complication.
*Objective.* To create a model for individual estimation of thrombosis risk during pregnancy and to determine the distribution of risk estimates in a series of gravidae.
*Method and patients.* Estimates of absolute risk of pregnancy-related thromboembolism were calculated by multiplying reported figures of thrombosis incidence by prevalence-adjusted odds ratios of the following variables: smoking, parity, preeclampsia, mode of delivery, age, overweight, activated protein C resistance (FV Leiden or FV:Q506), thrombosis heredity, and previous thrombosis. We present the risk distribution among a unselected prospectively gathered cohort of 2384 unselected gravidae who were interviewed and tested for activated protein C resistance in early pregnancy.
*Results and conclusions.* A model for individual estimation of the absolute risk of thrombosis is presented, which is provided to the readers as a free automatic Internet-based service (http://www.riskpreg.com). As compared with antepartum, more women at high risk can be identified in the postpartum period and we suggest that this might be of use in planning the prevention of thrombosis.

*Keywords:* risk estimation in pregnancy; prevalence of risk factors; logistic regression analysis; cesarean section; thrombophilia; thrombosis heredity; overweight

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Thromboembolic complications are a major contributor to maternal morbidity and mortality associated with pregnancy, accounting for around one-sixth of all maternal deaths in Sweden, the UK and USA (1–3). Thrombosis is estimated to occur in some 10–15 of 10 000 pregnancies in Western countries (4, 5).

Nowadays, women are usually classified as running either a high or a low risk (i.e. those with or without earlier thrombosis) of thrombosis in pregnancy. Women classified as 'high risk' are usually recommended heparin as a thrombosis prophylaxis during pregnancy, and heparin or warfarin in the postpartum period. This strategy may prevent the occurrence of renewed thrombosis, but does not prevent de novo thromboses. Women with a single risk factor such as a thrombophilia, thrombosis heredity, or overweight, usually still run a low risk of thrombosis. However, assessment of the thrombosis risk among women with a single risk factor or combinations thereof is not well established.

In this study we present a model for individualized estimation of the absolute risk of thrombosis in pregnancy and we present the risk estimates of the model on a prospectively gathered series of un-

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selected pregnant women to determine the distribution of risk in a general pregnant population.

## Methods

We assumed a multiplicative relationship between risk factors as indicated by earlier studies (6, 7). The risk at which initiation of thrombosis prophylaxis is indicated will presumably differ between the antepartum and the postpartum period. In addition, risk estimates of some variables (age, parity, and preeclampsia) have been shown to differ between these periods (4). Therefore, separate risk estimates were calculated for the antepartum and postpartum periods.

After entering a risk factor into the model, the summary risk of all women with or without this factor should be equal as before (prevalence adjustment). For example, the 9.8% women with cesarean delivery are associated with a fivefold increased risk of thrombosis. Thus the odds ratio (OR) for the remaining 90.2% of women with vaginal delivery might be estimated to be 0.72 ($0.098 \times 5 \times X \quad + 0.9 \times X = 1 = > X = 0.72$). Thus, the prevalence adjusted OR will be 0.7 for vaginal delivery and 3.6 for cesarean delivery (see Table I). Estimation of the absolute risk of thrombosis was performed by multiplying the prevalence adjusted OR of selected variables by the thrombosis incidence. The crude and prevalence-adjusted OR that we have included in the model are those given in Table I. For parity, smoking, preeclampsia and cesarean delivery, we used the adjusted OR reported in our population study, which was based on multivariate logistical regression analysis (4). The OR for heredity of thrombosis and obesity was approximated to be fivefold increased (8). Regarding heritable thrombophilia, we used a fivefold increased risk of heterozygous activated protein C (APC) resistance (8), and the same could be used for heterozygous protein C and protein S deficiencies (9). Thus, the OR for heredity of thrombosis, obesity, and APC resistance were based on univariate analysis. We decided to regard the homozygous carriers as having two heterozygous risks (i.e. $5 \times 5 = 25$-fold increased risk), which is close to the risk that might be calculated from the study by Svensson and coworkers (OR = 27.8) (10). Irrespective of other risk factors, women with earlier pulmonary embolism or other complicated thrombosis were set to have a 15% thrombosis risk and those with previous uncomplicated thrombosis were set at a risk of 10% (i.e. 5% antepartum and 5% postpartum) (11–13). If one factor included in the model was unknown, this factor was set to 1, and these cases remained included in the model. For example, in early pregnancy when the mode of delivery was unknown the OR was set to 1, and

Table I. Crude and prevalence adjusted odds ratios for risk of thrombosis during pregnancy and in the postpartum period

| | | Antepartum thrombosis | | Postpartum thrombosis | |
|---|---|---|---|---|---|
| | | Adjusted* | OR | Adjusted* | OR |
| APC resistance** | No | 1 | 0.7 | 1 | 0.7 |
| Heterozygosis | Yes | 5 | 3.4 | 5 | 3.4 |
| Homozygous | Yes | 25 | 16.8 | 25 | 16.8 |
| Overweight** | No | 1 | 0.7 | 1 | 0.7 |
| | Yes | 5 | 3.3 | 5 | 3.3 |
| Heredity of thrombosis** | No | 1 | 0.8 | 1 | 0.8 |
| | Yes | 5 | 4.1 | 5 | 4.1 |
| Age | $<20$ | 1.0 | 1.0 | 2.5 | 2.2 |
| | $\geq 20$ to $<35$ | 1.0 | 1.0 | 1 | 0.9 |
| | $\geq 35$ | 1.0 | 1.0 | 1.2 | 1.0 |
| Smoking** | No | 1 | 0.96 | 1 | 0.96 |
| | Yes | 1.2 | 1.2 | 1.2 | 1.2 |
| Parity | Nulliparous | 2.3 | 1.35 | 1.1 | 0.91 |
| | 1 child | 1 | 0.59 | 1 | 0.83 |
| | 2 children | 1.3 | 0.77 | 1.7 | 1.4 |
| | $>2$ children | 2.6 | 1.53 | 1.8 | 1.49 |
| Preeclampsia | No | | | 1 | 0.96 |
| | Yes | | | 3 | 2.9 |
| Caesarean delivery | No | | | 1 | 0.72 |
| | Yes | | | 4.9 | 3.6 |
| Earlier thrombosis*** | | | | | |

*Adjusted for estimated prevalence in our pregnant population; **The figures do not differentiate between ante- and postpartum venous thromboembolic event (VTE); ***There are no reliable data for odds ratios (OR) for women with earlier thrombosis. However, these women are reported to have a 5% absolute risk of ante- and postpartum thromboses.

did not influence the results. However, to estimate the postpartum risk of thrombosis at delivery, the OR had to be changed, depending on whether it was a cesarean or vaginal delivery (Table I).

We used the model to estimate the absolute risk of thrombosis in both the antepartum and postpartum periods in a previously prospective gathered unselected pregnant population (for detailed description see (8). Calculations were performed on all women who were delivered and included in the study group (2384 out of 2480) (6). The remaining 96 women had spontaneous or induced abortions. In three women with a previous history of venous thromboembolism, the presence of FV Leiden status was already known. In addition to eight women with a history of thrombosis, two more women were scheduled for anticoagulant prophylaxis because of a solid family history of thrombosis.

The definition of thrombosis was a deep venous thrombosis, pulmonary embolism, or cerebral thromboembolism occurring in pregnancy or during the first 3 months postpartum. Preeclampsia was defined as pregnancy-induced hypertension and proteinuria $>0.3$ g/l (albuminuria dipstick $\geq 1+$). Pregnancy-induced hypertension was defined as a resting diastolic blood pressure $>90$ mmHg measured on two occasions with an interval of at least 5 h, and developing after 20 weeks of gestation in a previously normotensive gravidity. Smoking habits were classified as either smoker or nonsmoker in early pregnancy (usually between 10 and 15 postmenstrual weeks). Overweight was defined as a maternal body mass index (BMI, kg/m) (2) exceeding 27.6, measured at the first visit to the antenatal health clinic, which is $>1$ standard deviation above the mean of our pregnant population (8). Thrombosis heredity was defined as one or more thromboses in first-degree relatives (father, mother or siblings) occurring before the age of 60 years (8). The estimated absolute risk is presented as the absolute risk out of 10 000 pregnancies.

As a result of the extremely skewed distribution of both risk estimates and the number at each categorized risk level, the figures were converted to their logarithms for the purpose of presentation. Descriptive statistics using median absolute risks with 95% confidence intervals (CI) were used. All statistical calculations were performed with SPSS software (SPSS Inc, Chicago, IL), and $P$-values $<$ 0.05 were considered statistically significant.

## Results

The distribution of estimated ante- and postpartum risk estimate-based anamnestic information, categorized into subgroups, is shown in Fig. 1. The eight women with earlier thromboembolic complications were at a risk of 500/10 000 for both antepartum and postpartum periods. As we studied women without a history of thromboemboism, these eight women are not included in the following discussion. As can be seen in Fig. 1, seven women (0.3% of women) were at 1+% absolute risk of thrombosis during the antepartum period and 21 women (0.9% of women) were similarly at risk during the postpartum period. When the APC resistance status was included in the calculations, the numbers (and percentages) of women at the 1, 2 and $\geq 5$% absolute risk levels during the antepartum period were 24 (1%), five (0.2%), and one (0.04%), and the respective postpartum figures were 13 (0.5%), nine (0.4%) and one (0.04%).

Including all risk factors, the five homozygotes who gave birth were found to be at a 4.3, 7.9, 9.9, 21 and $>100$% antepartum risk of thrombosis, and the corresponding postpartum risk figures were 3.2, 3.6, 4.0, 23 and $>100$%. Besides being homozygous APC-resistant, the last woman was overweight, had first-degree hereditary thrombosis and was delivered by cesarean section, as she had been in three out of four previous term pregnancies. Women without thromboembolic complications were found to be at a median 0.033% (95%CI, 0.014–0.33%) antepartum risk of thrombosis and a median 0.018% (95%CI, 0.013–0.48%)

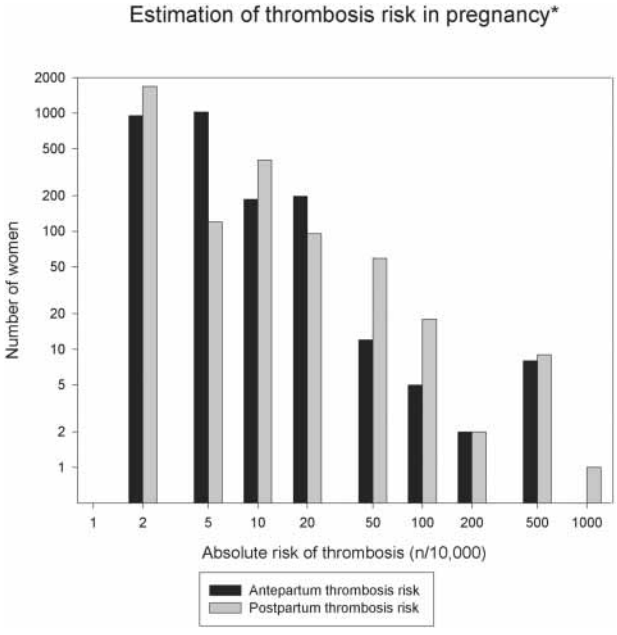


*Fig. 1.* Anamnestic data used to estimate the absolute risk of thrombosis included overweight, hereditary thrombosis, age, smoking, parity, preeclampsia, cesarean delivery, and former thromboembolic complications ($n=8$). Activated protein C resistance status was not included in this calculation.

postpartum risk. The three women with antepartum thromboembolic complications in their present pregnancy were at an antepartum risk (and postpartum risk) of 5% (5%), 0.76% (0.32%), and 0.03% (0.02%). The respective figures for the three women with postpartum complications were 0.2% (0.7%), 0.01% (0.6%), and 0.01% (0.2%). As a check for the model, the sum of all antepartum risk estimates was 2.1, and of postpartum risk estimates was 2.1, i.e. close to the number of thromboses in our study population.

## Discussion

The use of individual risk estimates might make it possible to determine the risk at which an anticoagulant is recommended in different situations, in place of the complex classification presently used, which classifies patients into high, low, and at times medium, risk groups. The distribution of the risk estimates might be of value for investigating the consequences of different strategies of thrombosis prophylaxis during pregnancy, or in the postpartum period. For research purposes the model might also be valuable for estimating the efficiency of treatment.

Few women could be identified as being at a 1% risk (or above) of antepartum thrombosis. However, three times as many were identified at this risk level during the postpartum period. As thrombosis prophylaxis could be initiated at a lower risk during the postpartum period, the aim of lowering de novo thrombosis might therefore be focused on the postpartum period.

Of the six women who developed thrombosis, one was already on thrombophrophylaxis because of a history of thrombosis, three were at a risk above 95% CI, and two women were at low risk. This supports, in part, the assumption of a multiplicative relationship between risk factors and risk of thrombosis. A drawback of the study is that the existence of a multiplicative relationship has not been shown for all included variables. In addition, in our multiplicative model women with multiple risk factors might be finish with unrealistic risk estimates, such as one woman who finished with a risk of more than 100%. However, we believe that even if risk estimates are approximate and at times impossible, they do give a more differentiated view compared with the currently used classification system. In order to test the generality of the model, a validation of the model on a large series of pregnant thrombosis cases is necessary.

In Sweden, women at high risk of postpartum thrombosis (i.e. $> 5\%$) are currently recommended 6 weeks of prophylaxis. As the risk of thrombosis is greatest in the immediate postpartum period, short-term prophylaxis may be discussed. Our model might be used to select women who are considered to be above a given risk level, instead of all women with cesarean delivery. Most of these women with cesarean delivery are still at low risk, and without other risk factors they have an approximate 0.15% risk of developing thrombosis. This means that approximately 650 women have to be treated in order to protect one woman from thrombosis. Women with risk-factor combinations might be at a much higher risk.

Several issues regarding thrombosis prophylaxis during pregnancy remain to be answered, viz, regarding the protective effect of low molecular weight heparin (LMWH) prophylaxis, the duration of the thrombosis prophylaxis for women with different degrees of risk, and safety aspects concerning delivery, such as the use of LMWH together with epidural anesthesia, and the rate of bleeding and osteoporosis complications following long-term LMWH.

The standard heparin treatment during pregnancy is known to be associated with 3% of serious complications (14). LMWH is thought to have fewer bleeding complications, but a recent study reported a four- to sixfold increased risk of bleeding complications during delivery among women receiving this prophylaxis (15). When compared to standard heparin, the risk of developing heparin-induced thrombocytopenia is lower with LMWH because of less platelet binding (16). However, this has yet not been shown during pregnancy. Furthermore, in future studies we need to decide at what level the benefits of prophylaxis outweigh the risks, during both pregnancy and postpartum. To determine these issues, large prospective studies will be needed.

We adjusted the OR to match the prevalence of each variable in our population. This is especially important regarding the mode of delivery (i.e. cesarean delivery, or not) and for a common hereditary thrombophilia such as APC resistance; factors present in large proportions of both the general population and thrombosis cases. If not, the risk estimates will be too high. This adjustment explains, in our study, the lowered proportion of women at 1% postpartum risk when the APC resistance status was included: the prevalence of APC resistance in the subgroup was lower than in the population. In the case of rare thrombophilias accounting for a small proportion of thromboses, the prevalence adjusted OR can be approximated by the crude OR. As we were unaware of the presence of other thrombophilias such as antithrombin deficiency, antiphospholipid syndrome, prothrombin A20210 polymorphism, etc., in our study group, and prospective studies of large series on

gravidae are nonexistent, we have not included them in our model. However, for practical purposes the OR of a nonincluded variable can be multiplied by the risk estimate obtained from the model (11, 12).

To conclude, we present a model for individual estimation of the absolute risk of thrombosis during pregnancy, having first applied it to a study population. We present our model to the reader as a free automatic Internet-based service (http://www.riskpreg.com).

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