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Postpartum blood transfusion and hemorrhage as independent risk factors for venous thromboembolism

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ABSTRACT

Introduction: Profuse postpartum hemorrhage (PPH) and red blood cell (RBC) transfusion have been suggested to be associated with venous thromboembolic events (VTE). However, it is not fully clear if they are independent major risk factors.

Methods: Women who gave birth in the Stockholm area between 1999 and 2002 were those studied, i.e., before the implementation of guidelines for thromboprophylaxis in pregnancy. In this population-based cohort study the Swedish Medical Birth Registry was linked to the National Discharge Registry and to the transfusion database. Cases with VTE were identified as well as the patient's transfusion history. The main outcome was an assessment of RBC transfusion and PPH as independent risk factors for postpartum thrombosis, analyzed in logistic regression models.

Results: Out of the 82,376 deliveries, 56 cases of postpartum VTE were identified (0.7‰). Compared to the control group, the risk of VTE increased with the number of RBC transfusions: 1 to 3 units (OR = 3.3, 95% CI 1.2–8.9) and > 3 units (OR = 5.2, 95%CI 1.7–16.1), but PPH was not found to be a major risk factor (OR = 1.4, 95% CI 0.5–3.5). Surprisingly, the small group treated with plasma in addition to RBC transfusion were not at a significantly increased risk (OR = 1.8, 95% CI 0.2–14.0). Preeclampsia and placental abruption were major risk factors.

Conclusion: We found RBC transfusion, but not PPH alone, to be an independent risk factor for postpartum VTE and propose that it should be included in the thromboprophylaxis algorithm for implementation during pregnancy.

1. Introduction

Pregnancy is a state of hypercoagulability that has most likely evolved over time to prevent women from fatal bleeding during childbirth [1]. However, this altered balance in coagulation also promotes an increased risk of thromboembolism during pregnancy [2]. Compared to non-pregnant women, the risk of venous thromboembolism (VTE) is increased by a factor of 5 to10 during pregnancy, and by a factor of 20 during the postpartum period. The incidence of VTE in relation to pregnancy is reported to be 1.3 to 1.7 per 1000 deliveries [2–4]. Pulmonary embolism (PE) is still a major contributor to maternal death and accounts for 1.1 deaths out of 100,000 maternities corresponding to approximately 8% to 17% of all maternal deaths in high resource countries [4–6]. There are several known maternal and pregnancy-related major risk factors associated with VTE, such as: previous thrombosis, thrombophilia, rheumatoid disease, inflammatory bowel diseases, obesity, immobilization, and high maternal age. Among pregnancy-related risk factors, ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, preeclampsia and cesarean delivery have been reported [2,4,7–11]. In recent years protocols and scoring systems involving low molecular weight heparin (LMWH) as thromboprophylaxis for women with a high risk of VTE have been implemented in obstetric care in many countries including the UK, the US, and Sweden [7,12,13]. In the UK maternal death from PE has decreased significantly from 1.5 in 100,000 to 0.7 in 100,000 after the introduction of a national guideline on thromboprophylaxis during pregnancy and the puerperium. However, the expected decrease in the frequency of VTEs during antenatal thromboprophylaxis has not yet been demonstrated, indicating a potential for improvement [7,14]. Both profuse postpartum hemorrhage (PPH) and transfusion of blood components have been suggested as possible risk factors for VTE in the postpartum period [4,6,9,10,14–16]. However, whether they are independent risk factors,

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and if or to what extent they should be implemented in existing guidelines for thromboprophylaxis postpartum, has not been concluded. Although thromboprophylaxis may save lives, it is costly and involves complications such as increased risk of bleeding and allergic reactions [17,18]. Therefore, in Sweden, a weighted risk estimation algorithm based on major risk factors (≈five-fold increased risk) was introduced in the year 2004 for identification of high risk candidates for thromboprophylaxis [13,19,20].

In this study, we aimed to investigate postpartum blood transfusion and PPH as potential and independent risk factors for postpartum VTE in a population prior to the thromboprophylaxis guidelines having been systematically introduced.

2. Methods

2.1. Study design and population

In this retrospective population-based cohort study we included all women who gave birth in the Stockholm area between 1999 and 2002. Reliable data on thromboprophylaxis after the implementation of the obstetric thromboprophylaxis guidelines was not available, and therefore we chose a period predating that implementation. Only women with a prior thromboembolic event (~0.3%) were then routinely considered for thromboprophylaxis [20]. By use of Sweden's unique personal identification number (PIN), data from the National Medical Birth registry (MBR) was linked to the Stockholm transfusion database and to the National Discharge Registry (NDR). The MBR was established in 1973 and information regarding the quality of the register has been published previously [21]. Reporting data to the MBR is mandatory and comprises information from early pregnancy, weight, height, parity, smoking habits, delivery details (such as diagnoses, gestational age at delivery, procedures, date of delivery), and outcome variables (such as APGAR score, fetal weight, and newborn diagnoses). Multiple pregnancies are noted and considered as a single case. Diagnoses of PPH and selected medical conditions and procedures were identified using International Classification of Diseases codes, 10th revision (ICD10) (Swedish version). The transfusion database contains data on all blood components and includes identification number, blood group, serial number of component, time of issue, and whether it was transfused [22]. Pregnant women who were hospitalized at least overnight are registered in the NDR, which contains data regarding diagnoses. The ICD10 codes used to identify cases of deep venous thrombosis in the postpartum period were O871, O873 or obstetric pulmonary embolism O882 occurring in, during or after delivery. By cross-matching MBR and NDR, it was possible to identify women who gave birth with a diagnosis of VTE from date of delivery and the six weeks following during the study period from 1999 to 2002.

Maternal age and body mass index (BMI) was dichotomized according to the present thromboprophylaxis guidelines (i.e., ≥40 years and BMI ≥ 30). Smoking was dichotomized into non-smoking and smoking during early pregnancy (daily smokers).

According to ICD10, PPH is defined as an estimated blood loss of > 1000 ml within 24 h from partus. By linking the MBR to the transfusion database all women who received blood transfusions at the time of delivery and for the next 24 h were identified, along with data on blood group, number of units of red blood cells (RBC), and plasma or platelets transfused. Postpartum anemia is defined as a hemoglobin value < 100 g/L on the second day after delivery. Ethical approval for the study was granted by the regional ethics board in Stockholm (Dnr: 2016/17-31/1).

2.2. Statistical analysis

Bivariate analysis with cross tabulations and its 95% confidence intervals (CI) and multiple logistic regression analysis were used to determine the relationship between the outcome variable (a postpartum VTE) and selected explanatory variables (RBC transfusion, PPH, high maternal age (≥40 years), high maternal BMI (≥30), blood group non-O, smoking, prior cesarean section (CS), multiple pregnancy, IVF, abruptio placentae, retentio placentae, placenta previa, preeclampsia, CS, fetal gender, birthweight, and preterm delivery (< 37 + 0). Variables with p-values < 0.1 and those known from prior studies were included as possible confounders in the initial multivariate analysis. RBC transfusion and PPH measure the same entity and both are known to be associated with placental pregnancy complications. In addition, women with preeclampsia are known to be at a three-fold increased risk for placental abruption [23]. Thus, several variables are dependent of each other and should not be included in the same adjusted analysis, due to the risk of over- or under estimation of true odds ratio (OR). Therefore, we created a dummy variable called "placental pregnancy complication" consisting of preeclampsia and/or placental abruption in the adjustments [23]. To avoid dependencies or interactions in evaluating the true risk of VTE in relation to RBC transfusion, plasma transfusion, PPH, postpartum anemia or placental complications, we created new dummy variables as necessary. In order to disentangle the dependencies, we proceeded step by step through six different logistic regression models to determine independent risk estimations [24]. In Model 1 these dummy variables included a) no transfusion or placental pregnancy complication (reference), b) only placental pregnancy complication, c/) only RBC transfusion, and d) both pregnancy complication and blood transfusion. Model 2 had as dummy variables a) no PPH or placental complication (reference) b) only placental complication, c) only PPH and d) both placental complication and PPH. Model 3 a) no RBC transfusion (reference), b) only 1 to 3 units of RBC, c) only > 3 units of RBC. Model 4 (main outcome) a) no PPH or RBC transfusion (reference), b) only PPH, c) 1 to 3 units of RBC transfusion, and d) > 3 units of RBC transfusion. Model 5 a) no RBC transfusion (reference), b) only RBC transfusion, and c) RBC and plasma transfusion. Finally, in Model 6 a) no postpartum anemia or RBC transfusion (reference), b) only postpartum anemia, c) 1 to 3 units of RBC transfusion, and d) > 3 units of RBC transfusion. Relative risks were estimated by ORs and 95% CIs. Absolute risks were calculated for the main variables investigated. All statistical calculations were performed using SPSS version 22 software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, US). P-values < 0.05 were considered statistically significant.

3. Results

During the study period from 1999 to 2002 we included a total of 82,376 deliveries in the Stockholm area and identified 56 cases of which 21 (38%) had PE. This represents a prevalence of postpartum VTE of 0.7 per 1000 deliveries. Characteristics of cases with postpartum VTE and the control population are presented in Table 1.

The VTE group had more twin pregnancies and a greater rate of high BMI (≥30). Among the VTE cases, 16% had received RBC transfusions and 20% were diagnosed with PPH. However, there were no significant differences between the groups in women > 40 years of age, smokers, IVF, or blood group non-O.

In Table 2 we evaluate the different models of assessing PPH and/or RBC transfusion as risk factors for postpartum VTE. We show that the choice of adjustment variables will influence the estimated ORs that RBC transfusion has on VTE. When not adjusting for pregnancy complications the risk estimate for VTE was 7.2 for RBC, when adjusting for both pregnancy complications and PPH the risk estimate was 3.0 (95% CI 1.2–7.9). Moreover, the risk estimates (OR) for PPH were not significant after adjusting for pregnancy complications and/or RBC transfusion.

In Table 3 we present six models each assessing the relationship between the selected variables. Model 1 indicates that both RBC transfusion and placental complications were major risk factors independent of each other having ORs of 5.1 and 7.0, respectively, and

Table 1
Demografics and clinical characteristics of women with a postpartum venous thrombembolicevent (VTE) and the background population.

Demografics and clinical characteristics	VTE		Control population		Bivariate
	N = 56	(%)	*N* = 82320	(%)	OR 95%CI
Age > 40 years	2	3.6%	2751	3.3%	1.1 0.3–4.4
BMI > 30[a]	8	14.3%	5094	6.2%	2.5 1.2–5.3
Smoking (n)	7	12.5%	6815	8.3%	1.6 0.7–3.5
Nulliparous	25	44.6%	38,931	47.3	0.9 0.5–1.5
Prior CS	5	8.9%	6422	7.8	1.2 0.5–2.9
Multiple pregnancy	3	5.4%	1139	1.4	4.0 1.3–12.9
In-vitro fertilization (n)	1	1.8%	1653	2.0	0.9 0.1–6.4
Blood group not 0	41	73.2%	51,113	62.1%	1.7 0.9–3.0
Placenta previa	0	0.0%	264	0.3%	na
Placental abruption	5	8.9%	292	0.4%	27.5 10.9–69.5
Preeclampsia	11	19.6%	2244	2.7%	8.7 4.5–16.9
Retentio placentae	4	7.1%	1886	2.3%	3.3 1.2–9.1
Postpartum anemia	15	26.5%	6007	7.3%	4.6 2.6–8.4
Mode of delivery					
Vaginal non-instrumental	23	41.1%	57,677	70.1%	0.3 0.2–0.5
Vaginal instrumental	6	10.7%	6404	7.8%	1.4 0.6–3.3
CS	25	44.6%	13,958	17.0%	4.0 2.3–6.7
PPH	11	19.6%	6500	7.9%	2.9 1.5–5.5
RBC transfusion	9	16.1	1967	2.4%	7.8 3.8–16.0
Plasma transfusion	2	3.6%	334	0.4%	9.1. 2.2–37.4
Platelet transfusion	1	1.8%	47	0.1%	32.5 4.4–240.0
Newborn characteristics					
Male newborn (n)	198	51.7%	119,049	51.4%	na
Birth weight newborn (≥4000 g)[b]	12	21.0%	16,223	19.8%	na
Gestational age at delivery (days)	272	24.0 SD	281	13.2 SD	na
Preterm delivery (n)	6	10.7%	6176	7.5%	na

VTE = Venous thromboembolic event, BMI = Body mass index, CS = Cesarean section. na = not applicable, PPH = Postpartum hemorrhage, RBC = Red blood cell. SD = Standard Deviation.
[a] BMI missing in 14,579 cases in control group.
[b] Birth weight missing in 352 cases in control group.

Table 2
Multivariate model of the risk of postpartum VTE by PPH and RBC transfusion. Illustrating crude risk (bivariate) and the effect of using different levels of adjustments on risk estimates (OR) for postpartum VTE.

Analysis of postpartum hemorrhage (PPH) and red blood cell (RBC) transfusion	Adjusted OR	95% CI
No PPH	1.0	Reference
PPH, crude risk	2.9	1.5–1.55
Adjustment[a]	2.7	1.4–5.2
Adjustment[b]	1.7	0.8–3.6
Adjustment[c]	1.2	0.5–2.7
No RBC transfusion	1.0	Reference
RBC transfusion, crude risk	7.8	3.8–16.0
Adjustment[a]	7.2	3.5–14.9
Adjustment[b]	3.3	1.5–14.9

VTE = Venous thromboembolic event, PPH = postpartum hemorrhage. RBC = Red blood cell, OR = Odds ratio, CI = Confidence interval.
[a] High age (< 40 years), BMI > 30, Multiple pregnancy, Blood group not 0.
[b] All above + preeclampsia, abruptio, CS and retentio placenta.
[c] All above and RBC transfusion.

the risk increased when the two were compounded (Fig. 1). Model 2 shows the same analysis, but with PPH instead of RBC transfusions. PPH alone was not found to be a major independent risk factor, and the two did not add to each other (Fig. 1). Model 3 points to a linear increased risk of VTE when a greater amount of RBC was transfused. The risk increased from three-fold with 1 to 3 units of transfused RBC to five-fold when > 3 units were transfused. The main result is presented in Model 4, where we separate "PPH only" and RBC transfusions as risk factors for VTE. In contrast to RBC transfusion, PPH alone was not shown to be a major independent risk factor for VTE. Model 5 women with RBC transfusion alone were compared to women with RBC transfusion with the addition of plasma. The latter group showed no significant increased risk of VTE. CS remained at a constant three-fold increased risk for VTE postpartum. The other adjusting variables were almost constant in the different models. The absolute risk for VTE among women with RBC transfusion was 5 per 1000 compared to 2 per 1000 after CS (Fig. 2). The highest risk for VTE postpartum was in women with both placental complications (preeclampsia and/or placental abruption) and RBC transfusion with a seventeen-fold increased risk.

4. Discussion

We found RBC transfusion in relation to delivery, but not PPH, to be a major independent dose-dependent risk factor for postpartum VTE. In accordance with a recent meta-analysis from Austria, CS was a major independent risk factor (OR 3) for postpartum VTE [25]. In addition, our results confirm that preeclampsia and placental abruption are also major independent risk factors for postpartum VTE. Our findings show the importance of taking the presence of preeclampsia, placental abruption, and CS into account to arrive at adequate risk estimates. To our surprise, in the subgroup with both RBC and plasma transfusion, which likely represents the most severe cases, the VTE risk was not significantly increased. Our study was not designed to evaluate the effect the addition of plasma may have on the risk of VTE. Cases with plasma were few and we had too low statistical power to draw any conclusion concerning the addition of plasma.

The large size of the study population and the accounting for all transfused units of blood components registered in an obligatory transfusion database, gave us the possibility to accurately reflect severe blood loss and transfusion of blood components at time of delivery. Since there are well-known dependencies and interactions between several risk factors for postpartum VTE, a major advantage was the unique ability to do separate analyses for the transfusion of RBC, plasma, PPH, and for placental complications (preeclampsia and placental abruption), as well as to make adjustments for other variables in order to determine their size and independence. Furthermore, the adjustments of CS and high BMI is an important factor and represents a major strength in order to obtain a more accurate OR.

While we do not have data on ongoing thromboprophylaxis, in attempting to minimize the bias of thromboprophylaxis, we chose a study period before the introduction of the present national obstetric thromboprophylaxis algorithm (Table S1). Our data shows lower risk estimates on postpartum VTE for CS and high BMI than previously reported, indicating that there may have been some thromboprophylaxis present [2].

This hospital based study does not have the same strength as a prospective randomized trial but it does have high statistical power due to its size. During the period studied, it was clinical practice to confirm a suspected VTE by imaging methods, i.e., spiral computer tomography (CT scans) for pulmonary embolism and ultrasound/compression blood flow or intravenous venography for usual deep vein thrombosis (DVTs). The cost of these examinations is covered by the national health care system. Therefore, we believe it is unlikely that DVTs were diagnosed without these imaging methods and that the risk of false positive cases is a low. During our study interval it was rare not to treat pregnant VTEs as in-patients. In a study by An-Ani and coworkers they showed ICD codes for identifying VTEs had a positive predictive value of 49%. This was mainly due to misclassification of remote VTEs, which is also common in Sweden [26]. Therefore, to reduce misclassification, we decided not to include out-patient cases. At that time it was very

1. **The risk increased from three-fold with 1 to 3 units of transfused RBC to five-fold when > 3 units w...**
Anchor Name: RBC transfusions as risk factors *[Agency Switzerland m.waldis@fatzerimbach.ch]*

Table 3
Logistic models attempting to estimate true Odds ratios (OR) for red blood cell (RBC) transfusion, amount of RBC, postpartum hemorrhage (PPH) and addition of plasma transfusion as risk factors for postpartum venous thromboembolic events (VTE).

Variable	Control group	VTE group	Adj Model 1–2		Adj model 3–5	
	n = 82,320	n = 56	OR	95% CI	OR	95% CI
Maternal characteristics/adjusting variables						
Age ≥ 40 (n)	2751	2	0.9	0.2–3.6	0.9	0.2–3.6
BMI > 30 (n)	5094	8	1.9	0.9–4.1	1.9	0.9–4.1
Multiple (n)	1139	3	1.8	0.5–5.9	1.8	0.5–5.9
Blood group non 0	51,113	41	1.7	0.9–3.0	1.7	0.9–3.0
Cesarean delivery (n)	13,958	25	2.8	1.6–5.0	2.9	1.6–5.1
Retentio placenta	1886	4	2.1	0.6–6.8	2.2	0.6–7.0
Preeclampsia/abruptio	2510	14			5.8	3.0–11.2
RBC transfusion (model 1)						
None	78,072	36	1.0	reference		
Preeclampsia/abruptio	2281	11	6.9	3–4-14.0		
RBC transfusion only	1738	6	4.9	1.9–13.0		
Preeclampsia/abruptio + RBC transfusion	229	3	16.1	4.7–55.5		
PPH (model 2)						
None	73,654	33	1.0	reference		
Preeclampsia/abruptio	2166	12	7.9	3.9–16.0		
PPH only	6156	9	2.2	0.99–4.9		
Preeclampsia/abruptio + PPH	344	2	7.1	1.6–31.2		
Amount of RBC transfusion (model 3)						
None	80,353	47			1.0	Reference
1–3 units RBC	1340	5			3.1	1.1–8.4
> 3 units RBC	627	4			4.9	1.6–15.2
PPH and RBC transfusion (model 4)						
None	75,364	42			1.0	Reference
PPH only	4989	5			1.4	0.5–3.5
1–3 units RBC	1340	5			3.3	1.2–8.9
> 3 units RBC	627	4			5.2	1.7–16.1
Combined transfusion (model 5)						
None	80,353	47			1.0	Reference
RBC transfusion only	1657	8			4.2	1.8–9.8
RBC and plasma transfusion	310	1			1.8	0.2–14.0
Postpartum anemia and RBC (model 6)						
None	75,862	39			1.0	reference
Postpartum anemia only	4491	8			2.2	0.98–4.7
1–3 units RBC	1340	5			3.6	1.3–9.9
> 3 units RBC	627	4			5.8	1.9–18.1

RBC = Red blood cell, PPH = Postpartum hemorrhage, VTE = Venous thromboembolic event.
Adj = Adjusted, OR = Odds ratio, CI = Confidence interval, BMI = Body mass index.
Adjusting variables are from model 1 and 3.
Model 4 consists of the variables; PPH without any RBC, 1 to 3 units of RBC and > 3 units of RBC the later two are irrespectable of PPH.

unusual to treat women with pregnancy VTEs as outpatients, and the risk of underestimating the incidence of VTEs can be said to have been low. A weakness of our study is that we do not have robust data on whether VTE events were first time thromboses.

The difference in risk of VTE between RBC transfusion, with or without PPH, and PPH alone might be that the more severe cases with profuse blood loss most likely involved RBC transfusion. In agreement with our findings, a dose dependent association between blood transfusion and VTE has been shown in colorectal cancer surgery [27].

Four previous studies have investigated RBC transfusion and its relation to VTE during pregnancy [4,6,14,16]. They report a wide range of ORs, presumably due to different adjusting modeling. In Table 2, we show a similar risk estimate (OR 7.2) as James and co-workers (OR 7.6) when not adjusting for pregnancy complications, and similar risk estimate (OR 3.0) as Abbasi and co-workers (OR 2.4) when adjusting for both PPH and RBC transfusion (dependent) [4,14]. In addition, the Abbasi study included VTE from the entire pregnancy and not exclusively postpartum events, which will underestimate the risk of postpartum thrombosis associated with blood transfusion in the peripartum period.

Women bleed whole blood but are transfused with concentrated blood (hematocrit 60% to 65%), which might not be physiological. Thus, there may be a factor of high viscosity of the transfused blood. Another explanation for the increased risk of VTE by RBC may be that the transfusion of stored erythrocytes itself affects coagulation. It has been suggested that transfusion of RBC units stored > 20 days increases the risk of VTE [28]. Stored units of RBC have been shown to have decreased levels of nitric oxide levels causing vasoconstriction, and increased lactate levels that result in a decreased pH and the release of proinflammatory cytokines, all affecting coagulation and enhancing hypercoagulability [29,30].

Although our study was not designed to analyze the combination of plasma and RBC transfusion, we included it in the post hoc analysis. Such instances represent the most severe cases with the greatest probability of impaired coagulation. The addition of plasma may affect the coagulation balance by adding both pro- and anticoagulants (such as antithrombin, protein C or protein S), which may be protective and decrease the risk of VTE. While this finding would benefit from more research, it is in agreement with the promising results from balanced transfusion protocols and suggests the merit of administrating plasma sooner in cases of obstetric hemorrhage requiring RBC transfusion.

Our finding that PPH without RBC transfusion is not associated with an independent increased risk of VTE contrasts with several previous studies reporting an OR of 1.4–9.0 [9,10,31,32]. In these studies the effect of RBC transfusion was not considered in the analysis, nor were there adjustments for CSs, preeclampsia, or placental abruption. The

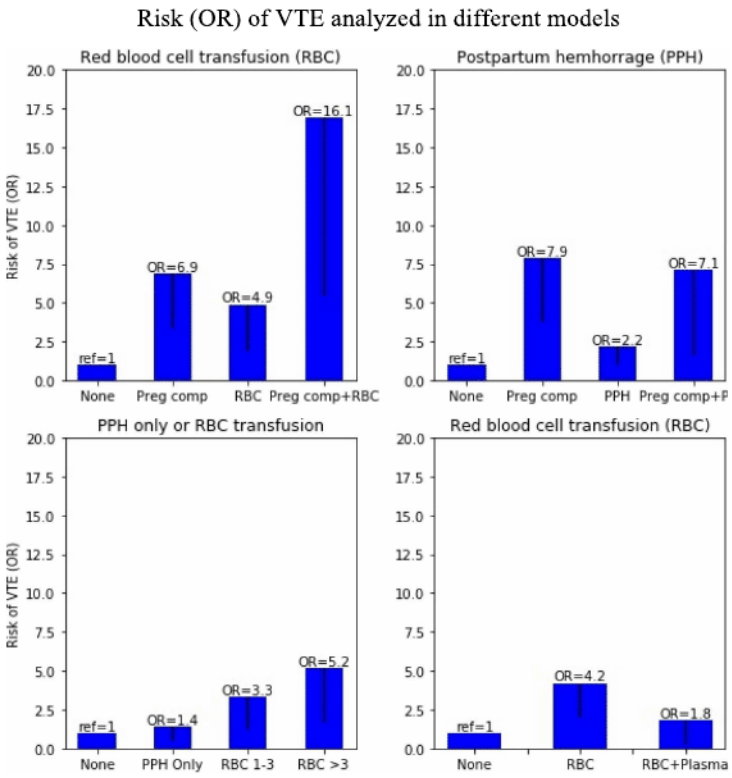

Fig. 1. Odds ratios (OR) and minus 95% confidence interval for the different regression models (1,2,4,5 in manuscript) in analyzing risk factors for postpartum venous thromboembolic events (VTE).
Ref = reference, Preg com = Pregnancy complication (preeclampsia and/or abruptio placenta).

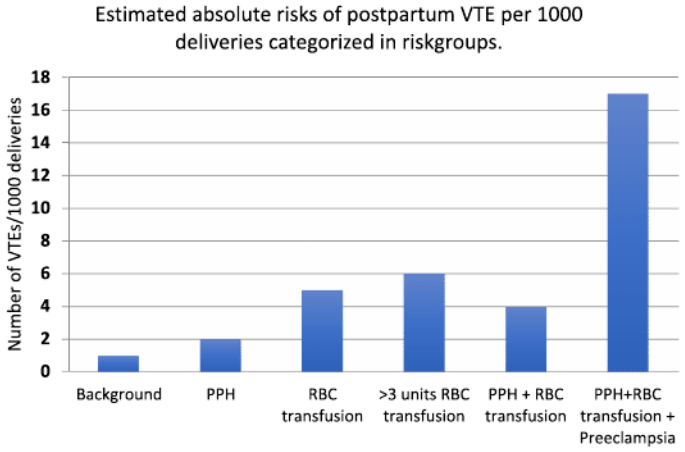

Fig. 2. Estimated absolute risks of postpartum VTE per 1000 deliveries categorized in different risk groups. VTE = Venous thromboembolic event, PPH = postpartum hemorrhage, RBC = Red blood cell.

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result may be an overestimation of the OR, as shown by our analysis in Table 2. In addition, not all studies were focused on events during delivery and the postpartum period [9,10].

Both preeclampsia and abruptio placenta have been included in the Swedish thromboprophylaxis guidelines as risk factors for postpartum, but not for antepartum VTE [2]. There has been a discussion regarding placental abruption and its association with the risk of VTE [23]. The large study by Liu and co-workers did not separate ante- and postpartum events, and no association between VTE and placental disorders (combining placenta previa and placental abruption) was found after adjustment. Placenta previa, in contrast to placental abruption, is not a risk factor associated with VTE. Thus, the combination of these variables might explain their lack of association with placental complications. The increased risk of postpartum VTE in preeclampsia is multifactorial, but one reason might be an induced low degree of disseminated intravascular coagulation causing low antithrombin levels seen in severe cases [33]. Plasma contains antithrombin and could have a protective affect against VTE in cases of preeclampsia.

Women with non-blood group O are at lower risk of bleeding but are reportedly at greater risk of preeclampsia and venous thrombosis [34]. It has been suggested that the increased risk of VTE is due to elevated levels of factor VIII, von Willebrand factor, and inflammatory cytokines [35]. We found non-blood group O to have a non-significant increased risk of VTE (70%).

It is known that IVF pregnancies are at an increased risk of antepartum thrombosis, which is to a large extent due to a very high risk of ovarian hyperstimulation syndrome (OHSS) [11,36]. There has also been discussion of whether IVF causes an increased risk of postpartum thromboses [37]. We found no support for this suggestion in the present study. Since IVF is related to placental pregnancy complications, advanced maternal age, more multiple pregnancies, and CSs, an unadjusted analysis may yield risk estimates for postpartum VTE that are too high.

In many recent studies, routine thromboprophylaxis is administered to patients after CS, which will change ORs [9]. It was not routine to administer low molecular weight heparin (LMWH) after CS during the period studied. The present routine is to recommend LMWH to cases of CS when other major risk factors are present (Table S1). At the time of our study, however, it was routine to administer LMWH thromboprophylaxis to women with prior VTE (~0.3% of the population) [20]. The national guideline in Sweden is a weighted major risk factor-based model showing at least a five-fold increased risk for VTE [19]. Minor risk factors (differences in risk < 2.5-fold), are not included in our algorithm whether they are significant or not. In addition, CS, preeclampsia, and abruptio placentae are already included as postpartum risk factors for VTE (Table S1). We have also decided to include RBC transfusion as a novel risk factor in the new Swedish guidelines conveying an approximately five-fold increased risk. The present thromboprophylaxis algorithm is found in Table S1.

Since we found RBC transfusion, but not PPH alone, to be an independent risk factor for postpartum VTE, we propose that it should be included in the Swedish thromboprophylaxis algorithm for implementation during pregnancy.

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Statement of conflict of interest

All authors declare no conflict of interest in relation to this work.

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Declarations of interest

None.

Précis

Transfusion of red blood cells is a major independent risk factor for postpartum thrombosis and should be included in the thromboprophylaxis algorithm during pregnancy.

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