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Full Length Article

# 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