THROMBOSIS AND HEMOSTASIS

# Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom

Alyshah Abdul Sultan,[1] Laila J. Tata,[1] Joe West,[1] Linda Fiaschi,[1] Kate M. Fleming,[1] Catherine Nelson-Piercy,[2] and Matthew J. Grainge[1]

[1]Division of Epidemiology and Public Health, University of Nottingham, City Hospital, Nottingham, United Kingdom; and [2]Women's Health Academic Centre, Guy's & St Thomas' Foundation Trust, St Thomas' Hospital, London, United Kingdom

## Key Points

- Antepartum, we found that established risk factors only had a modest effect on rates of VTE.
- Postpartum, we found that among other factors, women with stillbirth or preterm birth had high rates of VTE.

**Knowledge of the absolute risk (AR) for venous thromboembolism (VTE) in women around pregnancy and how potential risk factors modify this risk is crucial in identifying women who would benefit most from thromboprophylaxis. We examined a large primary care database containing 376 154 pregnancies ending in live birth or stillbirth from women aged 15 to 44 years between 1995 and 2009 and assessed the effect of risk factors on the incidence of antepartum and postpartum VTE in terms of ARs and incidence rate ratios (IRR), using Poisson regression. During antepartum, varicose veins, inflammatory bowel disease (IBD), urinary tract infection, and preexisting diabetes were associated with an increased risk for VTE (ARs, ≥139/100 000 person-years; IRRs, ≥1.8/100 000 person-years). Postpartum, the strongest risk factor was stillbirth (AR, 2444/100 000 person-years; IRR, 6.2/100 000 person-years), followed by medical comorbidities (including varicose veins, IBD, or cardiac disease), a body mass index (BMI) of 30 kg/m$^2$ or higher, obstetric hemorrhage, preterm delivery, and caesarean section (ARs, ≥637/100 000 person-years; IRRs, ≥1.9/100 000 person-years). Our findings suggest that VTE risk varies modestly by recognized factors during antepartum; however, women with stillbirths, preterm births, obstetric hemorrhage, caesarean section delivery, medical comorbidities, or a BMI of 30 kg/m$^2$ or higher are at much higher risk for VTE after delivery. These risk factors should receive careful consideration when assessing the potential need for thromboprophylaxis during the postpartum period. (*Blood*. 2013;121(19):3953-3961)**

## Introduction

Venous thromboembolism (VTE) is a rare but serious maternal complication. Despite its low absolute rate of 1 to 2 per 1000 maternities[1-4] during pregnancy and the puerperium, it remains a leading cause of maternal mortality in developed countries, as well as being an important source of morbidity in the form of post-thrombotic syndrome.[5] Universal thromboprophylaxis may not be cost effective or safe because of the risk for allergy and bleeding.[6] Therefore, routine thromboprophylaxis is recommended only for women considered at high risk for VTE on the basis of certain factors such as a previous VTE.[7] However, there is disagreement and inconsistency regarding the characteristics that put women at higher risk of developing a first VTE during pregnancy or postpartum combined with a lack of data about the relative effect of those risk factors with respect to the absolute risk for VTE. For example, existing estimates of the increase in risk for VTE among pregnant women with high BMI (⩾30 kg/m$^2$) compared with those with normal BMI range from 1.5-fold to 5.3-fold higher during antepartum and postpartum periods.[2,8-10] Similar inconsistencies surround women's demographic risk factors (eg, maternal age), comorbidities (eg, diabetes), and possible pregnancy complications (eg, mode of delivery, obstetric hemorrhage, and other complications),[2,3,8,10-15] particularly as many studies have inappropriately assumed that these risk factors similarly affect occurrence of VTE in the antepartum and postpartum periods.[2,8,10,14]

Of the studies that have separately assessed antepartum and postpartum VTE risks,[3,9,11,12,15] most have used a case-control design or relied on cross-sectional analysis of hospital discharge records based on risk factor information recorded around the time of delivery. Neither of these options enables estimation of absolute risk (AR) for VTE based on recognized risk factors during the entire period of gestation and immediately after childbirth. As a result, the current Royal College of Obstetricians and Gynecologists (RCOG)[7] and American College of Chest Physicians[16] guidelines on obstetric thromboprophylaxis are based on suboptimal information to distinguish between women who are at lower or higher risk. Therefore, the aim of this study was to determine population-level ARs and relative risks for VTE according to women's preexisting and pregnancy-related factors in both antepartum and postpartum periods, with the primary objective of allowing targeted provision of obstetric thromboprophylaxis. We also aimed to estimate specific ARs for VTE for women categorized as having low-, intermediate-, and high-risk pregnancies according to the United Kingdom's RCOG guidelines on who should receive prophylaxis.

Submitted November 23, 2012; accepted February 27, 2013. Prepublished online as *Blood* First Edition paper, April 2, 2013; DOI 10.1182/blood-2012-11-469551.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

**Table 1. Basic characteristics of women for each pregnancy**

| Variables | Pregnancies (N = 376 154 in 280 451 women) | Percentage |
|---|---|---|
| **Maternal characteristics** | | |
| Body mass index | | |
| Normal (18.5-24.9 kg/m$^2$) | 164 883 | 43.8 |
| Underweight (< 18.5 kg/m$^2$) | 12 309 | 3.3 |
| Overweight (25-29.9 kg/m$^2$) | 66 068 | 17.5 |
| Obese (≥30 kg/m$^2$) | 38 101 | 10.2 |
| Missing | 94 793 | 25.2 |
| Cigarette smoking | 88 617 | 23.5 |
| **Pregnancy-related characteristics and complication** | | |
| Birth outcome | | |
| Live birth | 375 002 | 99.7 |
| Stillbirth | 1152 | 0.3 |
| Mode of delivery | | |
| Spontaneous delivery | 294 426 | 78.3 |
| Caesarean | 58 109 | 15.5 |
| Assisted delivery | 23 619 | 6.3 |
| Previous live births | | |
| None | 213 697 | 56.8 |
| 1 | 116 351 | 30.9 |
| 2 | 33 819 | 8.9 |
| 3 or more | 12 287 | 3.4 |
| Multiple gestation | 6251 | 1.7 |
| Preterm delivery (< 37 wk) | 26 528 | 7.1 |
| Eclampsia/preeclampsia | 1897 | 0.5 |
| Obstetric hemorrhage | 4607 | 1.2 |
| Gestational hypertension | 6294 | 1.7 |
| Gestational diabetes | 2656 | 0.7 |
| Acute respiratory tract infection in pregnancy | 12 980 | 2.4 |
| Urinary tract infection in pregnancy | 30 765 | 8.1 |
| **Medical comorbidities** | | |
| Preexisting diabetes | 4022 | 1.0 |
| Preexisting hypertension | 11 718 | 3.1 |
| Varicose veins | 8373 | 2.2 |
| Nephrotic syndrome | 214 | 0.06 |
| Systemic lupus erythematosus | 188 | 0.05 |
| Cancer | 5012 | 1.3 |
| Inflammatory bowel disease | 1472 | 0.3 |
| Cardiac disease | 354 | 0.09 |

## Methods

The Health Improvement Network (THIN)[17] is an electronic database of medical records from more than 1500 general practitioners (GPs) and 429 UK practices. Approximately 98% of the UK population is registered with GPs, who are responsible for almost the entirety of a patient's medical care. All GPs participating in THIN are trained to record information using the general practice Vision software.[18] This software records individual-level data on diagnoses, prescription, lifestyle, and sociodemographic characteristics from all medical consultations. All data are then made anonymous before being added to the THIN database.[19]

Medical conditions and symptoms reported by patients to their GPs are recorded in the form of medical codes (Read codes), which are very comprehensive and use a hierarchal clinical classification system. These can be cross-referenced to the *International Classification of Diseases*.[20] Details on patients' secondary care referrals are obtained from hospital discharge forms, which contain details on inpatient and outpatient hospital admissions, including a summary of the main diagnoses and procedures undertaken. Prescription data in primary care are very well recorded, as the computerized system used by GPs to enter medications is also used to print the paper copy of the prescription to be presented at the pharmacy by the patient.

According to the National Institute for Health and Clinical Excellence guideline for antenatal care,[21] all pregnant women are required to undergo routine antenatal assessment to provide individualized care allowing primary care data to contain a comprehensive record of pregnancies in the United Kingdom. Both diagnoses of VTE[22] and fertility rates[23] have been validated with a high degree of accuracy in THIN or in the General Practice Research Database (GPRD), to which a number of practices in THIN also contribute. At the time of data analysis, THIN had information on 7.7 million patients who were broadly representative of the general UK population.

We identified all incident pregnancies ending in live birth or stillbirth for women aged 15 to 44 years who contributed data to THIN between January 1995 and July 2009. The pregnancy-related person time for each woman during the study period was divided into antepartum (from the date of conception to the pregnancy outcome) and postpartum (up to 12 weeks after the pregnancy outcome). This study was reviewed and approved by the THIN Scientific Review Committee (reference number 10-002R).

### Defining incident VTE

We identified all first VTEs including deep vein thrombosis or pulmonary embolism experienced by women (excluding superficial VTE) in our cohort. VTE cases and person time occurring within 1 month of the study start date were excluded to ensure that only incident cases were retained. As we were assessing only pregnancy-related VTE risk, only women without a prepregnancy history of VTE were included. VTE was based on a recorded medical code assigned by a physician and supplemented by evidence of anticoagulation prescription or a medical diagnosis indicating anticoagulant therapy within 90 days of the event or death within 30 days of the event date, as previously described in detail.[22,24] This definition has been previously validated with reasonable accuracy in a similar primary care database (GPRD), with 84% of all diagnoses confirmed on further investigation.

### Risk factors

***Basic characteristics.*** For each pregnancy, information on maternal factors during or before pregnancy was extracted from the patient's medical record. Maternal age was considered as a time-varying covariate assessed in 3 equal-sized categories (15-24, 25-34, and 35-44 years). Furthermore, information on BMI (the latest measure recorded by the GP before the date of conception) and smoking status (the latest measure recorded before delivery) was also extracted for each pregnancy.

***Pregnancy-related characteristics and complications.*** Pregnancy-related factors considered were mode of delivery, birth outcome (live or stillborn child), length of gestation, multiple gestation, and number of previous births. Pregnancy complications (including eclampsia/preeclampsia, hemorrhage, diabetes, and hypertension) were extracted using Read medical codes if they occurred during the pregnancy/postpartum period. Women were defined as having gestational diabetes if they had a first record of diabetes during pregnancy and no prior prescriptions for oral hypoglycemics or insulin. Gestational hypertension was defined as a medical code indicating the condition during pregnancy or at least 3 readings of high blood pressure after the second trimester (systolic, >140 mm Hg; diastolic, >90 mm Hg), with no antihypertensive treatment before pregnancy. We also separately investigated 2 common acute infections, urinary tract infection and acute respiratory tract infection (including pneumonia, acute bronchitis, chest infection, and influenza), during pregnancy.

***Medical comorbidities.*** Information on important comorbidities was extracted based on previous literature and the current RCOG guideline on thromboprophylaxis.[7] We defined women as having an existing relevant medical comorbidity if they had ever been diagnosed with cancer, systemic lupus erythematosus (SLE), or nephrotic syndrome or had recorded varicose veins, inflammatory bowel disease (IBD), or cardiac disease (including congestive cardiac disease, coronary artery disease, congenital heart disease, cardiomyopathy, angina, or myocardial infarction) during or before pregnancy. We also defined women as having preexisting diabetes or preexisting hypertension, using combinations of Read and prescription codes for such conditions before conception.

**Table 2. Absolute and relative rates of VTE by risk factors in the antepartum period**

| Variable | Events | Rate* | IRR† (Model 1) | IRR‡ (Model 2) |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Maternal age, y | | | | |
| 15-24 | 45 | 73 (54-98) | 0.87 (0.61-1.24) | 0.89 (0.62-1.27) |
| 25-34 | 120 | 79 (66-95) | 1.00 | 1.00 |
| 35-44 | 50 | 112 (85-148) | 1.42 (1.01-1.93) | 1.40 (0.99-1.96) |
| Body mass index | | | | |
| Underweight (<18.5 kg/m$^2$) | 3 | 34 (11-1074) | 0.48 (0.15-1.54) | 0.48 (0.15-1.53) |
| Normal (18.5-24.9 kg/m$^2$) | 86 | 73 (59-90) | 1.00 | 1.00 |
| Overweight (25-29.9 kg/m$^2$) | 49 | 103 (75-136) | 1.41 (0.99-2.00) | 1.40 (0.98-2.00) |
| Obese (≥30 kg/m$^2$) | 30 | 109 (76-156) | 1.50 (0.99-2.28) | 1.40 (0.90-2.16) |
| No BMI recorded before conception | 47 | 85 (63-113) | 1.18 (0.82-1.71) | 1.16 (0.85-1.69) |
| Cigarette smokers | 55 | 89 (68-116) | 1.15 (0.83-1.58) | 1.16 (0.84-1.60) |
| **Pregnancy-associated characteristics and complication§** | | | | |
| Previous live births | | | | |
| None | 127 | 90 (75-107) | 1.00 | 1.00 |
| 1 | 60 | 72 (56-93) | 0.76 (0.56-1.03) | 0.72 (0.53-0.98) |
| 2 | 19 | 78 (50-123) | 0.79 (0.49-1.28) | 0.71 (0.43-1.16) |
| 3 or more | 9 | 103 (53-198) | 0.97 (0.48-1.93) | 0.89 (0.45-1.78) |
| Multiple gestation | 3 | 73 (23-227) | 0.83 (0.26-2.61) | 0.83 (0.26-2.60) |
| Eclampsia/preeclampsia | 0 | — | — | — |
| Gestational hypertension | 4 | 95 (35-254) | 1.01 (0.37-2.76) | 0.99 (0.36-2.72) |
| Gestational diabetes | 3 | 165 (53-514) | 1.71 (0.54-5.41) | ‖ |
| Acute respiratory tract infection | 13 | 142 (82-245) | 1.70 (0.97-2.99) | 1.65 (0.94-2.90) |
| Urinary tract infection | 31 | 145 (102-206) | 1.88 (1.28-2.77) | 1.80 (1.22-2.67) |
| **Medical comorbidities§** | | | | |
| Preexisting diabetes | 8 | 282 (141-565) | 3.08 (1.42-6.39) | 3.54 (1.13-11.0) |
| Preexisting hypertension | 7 | 82 (39-173) | 0.90 (0.42-1.94) | 0.74 (0.32-1.71) |
| Varicose veins | 13 | 216 (125-373) | 2.69 (1.53-4.70) | 2.21 (1.55-4.76) |
| Nephrotic syndrome | 0 | — | — | — |
| Systemic lupus erythematosus | 0 | — | — | — |
| Cancer | 6 | 169 (76-373) | 1.97 (0.87-4.44) | 1.95 (0.86-4.41) |
| Inflammatory bowel disease | 3 | 288 (93-895) | 3.46 (1.11-10.7) | 3.50 (1.12-10.9) |
| Cardiac disease | 0 | — | — | — |

*Absolute rate calculated as per 100 000 person-years.
†Adjusted for age, parity, BMI, and smoking status when not stratified by them.
‡Adjusted for age, parity, BMI, preexisting diabetes, IBD, varicose veins, acute systemic infection, and smoking status when not stratified by them.
§IRR compared with women without risk factor under study.
‖Gestational diabetes was dropped from model 2 because of colinearity.

## Statistical analyses

We calculated absolute rates of VTE per 100 000 person-years by dividing the total number of events by the person-years of follow-up separately for antepartum and postpartum periods, which allowed us to directly compare risks per unit of time between antepartum and postpartum intervals.

To assess variations according to women's risk factors, we calculated absolute rates per 100 000 person-years for each maternal characteristic (eg, maternal age category), each pregnancy-related characteristic and complication (eg, each mode of delivery, obstetric hemorrhage etc), and medical comorbidities (eg, varicose veins, cardiac disease, etc), which were assumed to affect the whole pregnancy, regardless of when during the pregnancy they were recorded. For factors relating to labor or the puerperium (eg, mode of delivery), we only estimated absolute rates in the postpartum.

We then estimated incident rate ratios (IRRs) of VTE associated with each risk factor, using Poisson regression models that were adjusted for maternal age, body mass index (BMI), smoking status, and number of previous births (model 1). These adjustments were selected on the basis of previous literature. We also included risk factors that were associated with increased risk for VTE in our initial antepartum and postpartum analyses (model 2).

As pregnancies are not independent events, a clustering term was fitted in the models to account for women experiencing more than 1 pregnancy during the study period. Our study was sufficiently powered such that for a relatively rare risk factor that affects 1% of all pregnancies, we had greater than 90% power to detect a 2-fold increase (IRR, 2) in risk for VTE in both antenatal and postpartum periods separately.

The current UK RCOG guidelines for thromboprophylaxis during pregnancy and postpartum use a set of recognized clinical factors to categorize pregnant women as low, intermediate, or high risk during the antepartum and postpartum periods to guide which women are offered hydration/mobilization and which women are offered low–molecular weight heparin (LMWH) as thromboprophylaxis.[7] We estimated absolute rates of VTE, using the number of maternities as the denominator in this instance. This was done for each factor in isolation where possible.

In addition, we incorporated factors from our analysis that are not currently in the RCOG guideline but were highlighted in either the existing literature or this study (including preexisting diabetes, stillbirth, and preterm birth). These were placed in either the intermediate- or high-risk groups based on their absolute rate of VTE in this study. To ensure reasonable precision, we only calculated absolute rates for maternities in which 5 or more VTE events occurred among women with the risk factor. For this reason, SLE, cancer, nephrotic syndrome, cardiac disease, and IBD were grouped together, as current guidelines indicate that women with any of these risk factors should be considered for prophylaxis.

Pregnancies complicated by medical comorbidities in which there were no VTE events (eg, nephrotic syndrome) during the antepartum and/or postpartum periods were still included in the analysis so as to

**Table 3. Absolute and relative rates of VTE by risk factors in the postpartum period**

| Variable | Events | Rate* | IRR† (Model 1) | IRR‡ (Model 2) |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Maternal age, y | | | | |
| 15-24 | 48 | 255 (192-339) | 0.80 (0.57-1.12) | 0.86 (0.62-1.00) |
| 25-34 | 156 | 316 (270-370) | 1.00 | 1.00 |
| 35-44 | 81 | 497 (399-618) | 1.51 (1.15-1.98) | 1.37 (1.23-3.01) |
| Body mass index | | | | |
| Underweight (<18.5 kg/m$^2$) | 4 | 145 (54-386) | 0.63 (0.23-1.71) | 0.61 (0.22-1.67) |
| Normal (18.5-24.9 kg/m$^2$) | 88 | 237 (192-292) | 1.00 | 1.00 |
| Overweight (25-29.9 kg/m$^2$) | 48 | 324 (244-429)) | 1.33 (0.93-1.89) | 1.29 (0.90-1.83) |
| Obese (≥30 kg/m$^2$) | 79 | 926 (742-1554) | 3.75 (2.76-5.08) | 3.45 (2.54-4.69) |
| No BMI recorded before conception | 66 | 305 (239-390) | 1.40 (1.01-1.92) | 1.46 (1.06-2.01) |
| Current smokers | 80 | 403 (324-504) | 1.31 (1.01-1.71) | 1.30 (1.00-1.69) |
| **Pregnancy-related characteristics and complication§** | | | | |
| Mode of delivery | | | | |
| Spontaneous | 186 | 281 (243-325) | 1.00 | 1.00 |
| Assisted | 16 | 302 (185-494) | 1.18 (0.70-1.99) | 1.22 (0.73-2.06) |
| Caesarean | 83 | 637 (513-790) | 1.99 (1.52-2.58) | 1.88 (1.44-2.45) |
| Previous live births | | | | |
| None | 152 | 318 (271-373) | 1.00 | 1.00 |
| 1 | 75 | 285 (228-358) | 0.81 (0.61-1.08) | 0.82 (0.62-1.09) |
| 2 | 33 | 432 (307-608) | 1.13 (0.77-1.66) | 1.08 (0.73-1.60) |
| 3 or more | 25 | 904 (611-608) | 2.07 (1.34-3.20) | 1.92 (1.22-2.99) |
| Stillbirth | 6 | 2444 (109-5440) | 6.24 (2.77-14.1) | 4.07 (1.73-9.56) |
| Multiple gestation | 7 | 491 (234-1030) | 1.39 (0.65-2.93) | 0.94 (0.43-2.07) |
| Preterm birth | 51 | 854 (649-1124) | 2.69 (1.99-3.65) | 2.28 (1.66-3.14) |
| Preeclampsia/eclampsia | 3 | 705 (227-2188) | 1.84 (0.59-5.78) | 1.17 (0.36-3.77) |
| Obstetric hemorrhage | 10 | 963 (518-1791) | 2.89 (1.53-5.43) | 2.53 (1.34-4.79) |
| Gestational diabetes | 6 | 1013 (455-2255) | 1.97 (0.87-4.45) | 1.68 (0.74-3.82) |
| Gestational hypertension | 10 | 705 (379-1311) | 1.63 (0.85-3.12) | 1.49 (0.78-2.84) |
| Acute respiratory tract infection | 18 | 617 (389-980) | 1.65 (1.02-2.66) | 1.56 (0.97-2.53) |
| Urinary tract infection | 27 | 391 (268-571) | 1.15 (0.77-1.71) | 1.06 (0.71-1.58) |
| **Medical comorbidities§** | | | | |
| Preexisting diabetes | 4 | 445 (167-1186) | 0.88 (0.33-2.38) | 0.69 (0.25-1.85) |
| Preexisting hypertension | 3 | 113 (36-353) | 0.25 (0.81-0.79) | 0.22 (0.71-0.68) |
| Varicose veins | 25 | 1330 (899-1969) | 3.83 (2.51-5.82) | 3.90 (2.56-5.93) |
| Nephrotic syndrome | 0 | — | — | — |
| Systemic lupus erythematosus | 1 | 2374 (344-16856) | 6.69 (0.95-47.0) | 5.40 (0.76-38.3) |
| Cancer | 5 | 446 (185-1073) | 1.21 (0.49-2.96) | 1.14 (0.46-2.79) |
| Inflammatory bowel disease | 5 | 1514 (630-3638) | 4.56 (1.88-11.0) | 4.07 (1.73-9.57) |
| Cardiac disease | 2 | 2258 (646-10335) | 6.58 (1.63-26.5) | 5.30 (1.30-21.5) |

*Absolute rate calculated as per 100 000 person-years.

†Adjusted for age, parity, BMI, and smoking status when not stratified by them.

‡Adjusted for age, parity, BMI, mode of delivery, pregnancy length, obstetric hemorrhage, varicose veins, IBD, cardiac disease and smoking status when not stratified by them.

§IRR compared with women without risk factor under study.

contribute to the denominator for calculating the incidence rate for VTE, but they were not investigated individually. In addition, high BMI (≥30 kg/m$^2$) was separated into obese (BMI ≥ 30 Kg/m$^2$ and BMI < 40 kg/m$^2$) and class 3 obese (BMI ≥ 40 kg/m$^2$) categories, whereas acute respiratory tract and urinary tract infections were collectively assessed as stated in the current thromboprophylaxis guideline.[7] All analyses were carried out using Stata SE11 (Statacorp, College Station, TX).

## Results

### Basic characteristics

Among 280 451 women who had 1 or more pregnancies in our cohort, there were 376 154 pregnancies resulting in live births or stillbirths. Women's basic characteristics for each pregnancy are summarized in Table 1. The overall incidence of VTE during the antepartum and postpartum periods was calculated to be 84 and 338 per 100 000 person-years, respectively.

### Risk factors for VTE during the antepartum period

The relative risk for VTE during antepartum was only marginally higher for women aged 35 years or older, women with a BMI of 30 kg/m$^2$ or higher, and women who were cigarette smokers, corresponding to a 42%, 50%, and 15% increased risk, respectively, compared with baseline (Table 2). Of the pregnancy-related characteristics and complications, only urinary tract infection was found to be significantly associated with an increased risk for VTE (88% increase in risk). However, medical comorbidities, including preexisting diabetes, recording of varicose veins, and IBD (but not preexisting hypertension or cancer), were all associated with higher rates of VTE, with absolute rates ranging from 216 (varicose veins) to 288 (IBD) per 100 000 person-years. Our IRRs for risk factors

**Obstetric thromboprophylaxis risk assessment and management guidelines**

**Block 1 (High risk factors)**
×-Single previous VTE+ Thrombophilia
Unprovoked previous VTE
×-previous recurrent VTE (>1)

→ **Antenatal thromboprophylaxis with LMWH**
**No data from current study**

**Block 2**
**Intermediate risk factors**
×-Single previous VTE with no family history or thrombophilia
x-Thombophilia + no VTE
√-Medical co-morbidities (SLE, Cancer, IBD, cardiac disease or nephrotic syndrome)
×-Sickle cell
×-Intravenous drug users
×-Surgical procedure
◊-Pre-existing diabetes

→ **Any 1 Factor (may be accompanied by other risk factors in block 3 but not block 2)**
**Antenatal thromboprophylaxis with LMWH**

| Variable | Events | Rate (95% CI) |
|---|---|---|
| Medical co-morbidities | 9 | 130 (72-371) |
| Pre-existing diabetes | 7 | 180 (72-371) |
| Any 1 risk factor | 18 | 165 (97-260) |

**Block 3**
**Low risk factors**
√-Age ≥ 35
√-Obese BMI≥ 30Kg/m$^2$
√-Previous births≥ 3
√-Cigarette smokers
√-Eclampsia/preeclampsia
√-Acute systemic infection
√-Varicose veins
×-Any surgical procedure
×-Prolong labour (>24 hours)
×-Mid-cavity rotational operation
×-Immobility
×-Dehydration
√-Multiple pregnancy

→ **Figure**
**Antenatal thromboprophylaxis with LMWH**

| Variable | Events | Rate (95%CI) |
|---|---|---|
| Two or more risk factors | 47 | 95 (69-125) |

→ **1 factor with no other risk factors in block 2 and 3**
**Mobilisation and hydration**

| Variable | Events | Rate (95%CI) |
|---|---|---|
| Age ≥ 35 | 23 | 70 (44-104) |
| BMI ≥ 30 | 7 | 42 (16-85) |
| Previous births≥ 3 | 3 | 92 (18-268) |
| Cigarette smokers | 24 | 44 (27-64) |
| Varicose veins | 5 | 149 (48-346) |
| Acute systemic infection | 13 | 65 (24-11) |
| Any one risk factor | 75 | 55 (43-69) |

Key
√ Factor is included in the current thromboprophylaxis guideline and in current study analysis
×Factor is included in the current thromboprophylaxis guideline but not included in the current study analysis
◊ Factor is included in the study analysis but is not in the current thromboprophylaxis guidelines
LMWH= Low molecular weight heparin

**Figure 1. Rate of VTE per 100 000 pregnancies during the antepartum, according to the national guideline.[7]**

remained unchanged when mutually adjusted for other risk factors associated with an increased risk for antepartum VTE (model 2).

### Risk factors for VTE during the postpartum period

In the postpartum period, we found a 4-fold increased risk for VTE in women with a BMI of 30 kg/m$^2$ or higher (IRR, 3.75; 95% confidence interval, 2.76-5.08) compared with those with normal BMI (Table 3). However, the rate of VTE was only moderately higher for other maternal characteristics, including age 35 years or older and smoking status, when compared with baseline.

For pregnancy-related characteristics and complications, we found a 2-fold or greater increase in the rate of VTE compared with baseline for those with caesarean delivery, 3 or more previous births, obstetric hemorrhage, and preterm (<37 weeks) delivery (with absolute rates ranging between 637 and 963/100 000 person-years). Pregnancy ending in stillbirth was associated with a 6-fold increase in the rate of VTE compared with a live-birth outcome (absolute rate, 2444 VTEs/100 000 person-years), with rates associated with medical comorbidities (including varicose veins, IBD, and cardiac disease) ranging from 1330 to 2258 VTEs/100 000 person-years. When including all risk factors associated with an

**Obstetric thromboprophylaxis risk assessment and management guidelines**

**Block 1 (High risk factors)**
◊ -Still births
× -Previous VTE
× -Antenatal VTE

**Factor may be accompanied by other risk factors in block 2 and 3**
**6 weeks postnatal thromboprophylaxis**

| Variable | Events | Rate (95%CI) |
|---|---|---|
| Stillbirths | 6 | 523 (192-1135) |

**Block 2**
**Intermediate risk factors**
√ -Caesarean section delivery[1]
√ -Very obese BMI ≥ 40Kg/m$^2$
x-Thrombophilia
◊ -Preterm birth
√ -Medical co-morbidities (SLE, Cancer, IBD, cardiac disease or nephrotic syndrome)
√ -Obstetric Haemorrhage
× -Surgical procedures
× -Intravenous drug users
× -Sickle cell disease
× -Prolonged hospital admission

**Any 1 Factor (may be accompanied by other risk factors in block 3 but not block 1 or 2)**
**7 days postnatal thromboprophylaxis with LMWH**

| Variable | Events | Rate (95% CI) |
|---|---|---|
| Caesarean section | 49 | 101 (75-134) |
| BMI ≥ 40Kg/m2 | 6 | 221 (81-481) |
| Medical co-morbidities | 7 | 137 (55-282) |
| Premature birth | 22 | 121 (76-184) |
| Haemorrhage | 5 | 154 (50-361) |

**Block 3**
**Low risk factors**
√ -Age ≥ 35
√ -Obese (BMI ≥ 30Kg/m$^2$ & BMI<40Kg/m$^2$)
√ -Previous births ≥ 3
√ -Cigarette smokers
√ -Eclampsia/preeclampsia
√ -Acute systemic infection
√ -Varicose veins
× -Any surgical procedure
× -Prolong labour (>24 hours)
× -Mid-cavity rotational operation
× -Immobility

**≥2 factors with no other risk factors in block 1 and 2**
**7 days postnatal thromboprophylaxis with LMWH**

| Variable | Events | Rate (95%CI) |
|---|---|---|
| Two or more risk factors | 41 | 111 (80-151) |

**1 factor with no other risk factors in block 1, 2 and 3**
**Hydration and mobilisation**

| Variable | Events | Rate (95%CI) |
|---|---|---|
| Age ≥ 35 | 14 | 44 (24-75) |
| BMI ≥ 30 & < 40Kg/m$^2$ | 16 | 143 (82-233) |
| Previous births ≥ 3 | 2 | 78 (9-284) |
| Cigarette smokers | 17 | 38 (22-61) |
| Varicose veins | 5 | 188 (61-440) |
| Acute systemic infection | 5 | 32 (10-75) |
| Any one risk factor | 61 | 56 (43-72) |

Key
√ Factor is included in the current thromboprophylaxis guideline and in current study analysis
× Factor is included in the current thromboprophylaxis guideline but not included in the current study analysis
◊ Factor is included in the study analysis but is not in the current thromboprophylaxis guidelines
[1]Includes elective and emergency caesarean section
LMWH= Low molecular weight heparin

**Figure 2. Rate of VTE per 100 000 pregnancies during the postpartum, according to the national guideline.[7]**

increased risk for VTE in our regression model (model 2), our estimates remained broadly similar.

### Risk for VTE per 100 000 pregnancies according to the UK's ROCG guideline

Figures 1 and 2 contain the risk factors currently listed in the RCOG guideline[7] for antepartum and postpartum thromboprophylaxis, with the addition of preexisting diabetes (antepartum), stillbirth, and preterm birth (both postpartum only). We found that among women who were classed as being at intermediate risk for antepartum VTE on the basis of a single risk factor, the highest risk for VTE was 180/100 000 pregnancies for women with preexisting diabetes (Figure 1). Postpartum women with a BMI of 40 kg/m$^2$ or higher had a higher risk for VTE (absolute rate, 221/100 000 pregnancies)

than those women with any other single intermediate risk factor (preterm birth, prior medical comorbidities, caesarean delivery, and hemorrhage; Figure 2). Of factors currently used to classify women as low risk for postpartum VTE if occurring in isolation (ie, those whom are offered nonpharmacological thromboprophylaxis, including early mobilization and hydration), high risks for VTE were observed for women with a BMI between 30 and 40 kg/m$^2$ (absolute rate, 143/100 000 pregnancies) and varicose veins (absolute rate, 188/100 000 pregnancies) in the absence of other risk factors. The risk for VTE, however, in the postpartum after stillbirth was calculated to be 0.5%, which was higher than any other risk factor.

## Discussion

In this large, nationally representative cohort of almost 400 000 pregnancies, we have provided population-based estimates of the AR and relative risk for VTE in women during and immediately after pregnancy, combining their sociodemographic, lifestyle, and clinical risk factors to better inform targeting of thromboprophylaxis. We have demonstrated that except for preexisting diabetes, risk factors have a greater effect in the postpartum period in terms of influencing the AR for VTE than in the antepartum period. We also found that women with stillbirths, obstetric hemorrhage, high BMI, preterm birth, prior comorbidities (IBD and cardiac disease), and caesarean delivery have substantially higher risk for VTE postpartum. In contrast, cigarette smoking, maternal age 35 years or older, acute infection, and number of previous births were only moderately associated with VTE in both the antepartum and postpartum periods.

The use of nationally representative data not only makes our study findings generalizable to the majority of the pregnant women in the United Kingdom (ie, those who have not had a prior VTE) but also provides information on risk factors for VTE in a contemporary and population-based manner. Most previous studies have relied on cross-sectional analyses of hospital discharge records collected around the time of delivery,[2,10,15] were unable to separate first from subsequent VTE,[2,3,15] and relied on retrospective recall of risk factor information.[8,12,13] In contrast, our open-cohort approach to analysis and prospective nature of data recording enabled us to look at the effect of existing and pregnancy-related risk factors on the incidence and relative risk for VTE separately for the antepartum and postpartum periods.

A potential limitation of our study is the lack of validation studies of obstetric complications in our data set and the scarcity of national UK or international data estimating the true prevalence of obstetric complications in the general population. Although all major medical events in secondary care should be recorded in the general practice notes, minor complications that are well managed in the hospital setting may not be recorded in primary care data. For instance, the estimated prevalence of obstetric hemorrhage ranges from 2% to 8%, with the prevalence of severe hemorrhage estimated to be between 0.01 and 1.86%.[25-27] We found a prevalence of 1% in our study, which indicates our cases are more likely to represent severe hemorrhage (the same may be the case for gestational hypertension and preeclampsia).

We also acknowledge that certain risk factors including mild to moderate preeclampsia might not always get reported in the hospital discharge summaries that are sent to GPs, thus underestimating their prevalence.[28-31] In particular, residual confounding caused by the underascertainment of preeclampsia could have accounted for some of the postpartum effect we observed for stillbirths and preterm births. However, around 50% of stillbirths are unexplained.[32]

In our study, none of the 6 women with stillbirth who developed VTE had recorded coexisting medical risk factors or pregnancy-associated complications. We do acknowledge that we were not able to assess certain parameters, including mother's ethnicity and fertility treatments that may often be associated with increased risk for VTE. However, we believe that the following should be considered: 91%[33] of the UK population is white, which we believe would have limited the effect of confounding by race on our estimates, and in addition, a case–control study from the UK showed no association between antenatal pulmonary embolism and ethnicity.[13] Also, the overall reporting of fertility problems in the United Kingdom, using primary care data,[34] is reported to be 0.5% per annum, with an infertility treatment rate of 0.1% per annum. Moreover, the actual number of women conceiving after treatment may be even lower, although we were not able to evaluate this in our data. This depicts the limited scope of this variable to modify our conclusions from these data.

A few other aspects of our data are worthy of note. Our data relied on BMI measured before pregnancy, in line with most existing research. However, a previous study found that weight gain during pregnancy was a more important predictor of VTE risk,[12] something we were unable to assess. Our finding of a high risk for VTE in those with a prior diagnosis of varicose veins should also be interpreted with caution, as it may potentially be a consequence of a past unrecorded or concurrent deep vein thrombosis. Finally, we were not able to assess thrombophilia as a potential risk factor in our study. We believe that a diagnosis of thrombophilia cannot be used to predict VTE outcome, as routine thrombophilia screening is not recommended for pregnant women.

Our definition of VTE had a positive predictive value of 84% when validated among women of childbearing age in the GPRD,[22] a UK primary care database to which a large proportion of the practices in THIN also contribute. Such validation, however, does not give an indication of the negative predictive value (or sensitivity), and we cannot ignore the potential for our absolute rates of VTE to be underestimated if some anticoagulant prescriptions emanated from secondary, rather than primary, care. Despite this, Huerta et al[35] reported an age- and sex-standardized incidence rate of VTE using the GPRD that was similar to that observed in other Western studies when using a VTE definition identical to that of the present analysis.

It may be argued that our estimates do not take into account the number of pregnant women already receiving thromboprophylaxis before a VTE event. Although we excluded women with prior history of VTE from our study, we found that 0.4% of pregnant women without VTE received heparin/LMWH prescribed by a GP during the antepartum/postpartum period (also included in the analysis), which may be a result of certain clinical risk factors, as suggested in the current RCOG guideline. This, however, is certainly an underestimate, as we were unable to look at thromboprophylaxis prescriptions emanating from secondary care. We believe though that the effect of this would be small, as the first national RCOG guidelines for antenatal thromboprophylaxis were only published in 2004, with an updated version published in 2009. In the light of this fact, we calculated the risk for VTE during pregnancy and postpartum pre- and post-2004, which showed no statistical difference in the postpartum and a 46% (statistically significant) increase in the risk for VTE post-2004 in the antepartum period, suggesting a minimal effect of the national guidelines on the incidence of VTE.

We should also emphasize that assessing the effectiveness of the current national guidelines for obstetric thromboprophylaxis is beyond the scope of this study. One way of assessing this could be calculating the number needed to treat (NNT) and number needed to harm from our data. For instance, if we were to assume that prophylaxis reduces the risk for VTE by 50%, as has been reported in trials outside of pregnancy,[36] then based on our estimate of the AR, 89 VTE events could be prevented per year in women whose pregnancies end in caesarean delivery (NNT, 1980). These values should be interpreted with caution, as they are based on speculative data regarding the reduction in risk resulting from LMWH, from which there is an absence of RCT data in pregnant women.

Our relative increases in the risk (more than 2-fold) of VTE in those with preterm birth, obstetric hemorrhage, caesarean delivery, stillbirth, and varicose veins compared with women without those respective risk factors are of roughly similar magnitude to those reported in other studies.[2,3,8,10,12,15,37] We believe that the strong association between VTE events and stillbirths we observed is a finding of real importance that has received only limited attention to date.[37] Our finding of low relative increases in the risk for VTE among women aged 35 years or older, current smokers, and those with high BMI during the antepartum period are also in concordance with previous studies.[3,10,15]

## Clinical implications

Our results may have important implications for the way obstetric thromboprophylaxis is delivered in the healthcare settings of developed countries, and we hope that they will aid the targeting of such prophylaxis in 3 ways.

First, we found an increased risk for VTE among pregnancies of women with preterm birth or stillbirth, factors that have received limited consideration to date and are not currently incorporated in the guidelines for risk assessment of VTE. If they were incorporated, then thrombotic events associated with those risk factors could potentially be prevented.

Second, our data support many of the existing national RCOG guideline recommendations (in terms of high absolute rates), especially that postpartum thromboprophylaxis may be indicated in women with very high BMI ($\geq$40 kg/m$^2$), those who have prior comorbidities, those who have obstetric hemorrhage, or those who have a caesarean delivery.

Third, our results showed a high risk for VTE in women with a BMI between 30 and 40 kg/m$^2$ or varicose veins, even if these risk factors occur in isolation, which may require careful consideration. The recommendation on whether thromboprophylaxis with LMWH may be effective in pregnant and postpartum women with the above highlighted risk factors will of course highly dependent on the risk reduction from prophylaxis, for which there is a noticeable void of data from pregnant women.

Another important consideration is the costs involved in prophylaxis, both financial and in terms of the tolerability surrounding a daily heparin prescription, not to mention the well-recognized adverse effects of allergy and bleeding. For instance, the benefits would need to be weighed against a risk for major hemorrhage, which is believed to occur in 1% of pregnant women.[16] Such a risk–benefit analysis clearly goes beyond the scope of the present work; however, we believe our presentation of population-based risks for VTE, based on a number of established risk factors, goes some way to helping clinicians involved in making decisions in this area.

In summary, our study provides new and interesting observations on the absolute rate of VTE in a range of categories of pregnancy and postpartum period. It provides valuable information to clinicians for better decision making in terms of identifying high-risk pregnant and postpartum women who may require some form of thromboprophylaxis.

## Authorship

Contribution: A.A.S., J.W., and M.J.G. conceived the idea for the study, with L.J.T. and K.M.F. also making important contributions to the design of the study, which used a data set created by L.J.T. and L.F. linking maternal records from the THIN database to those of their offspring; A.A.S. carried out the data management and analysis and wrote the first draft of the manuscript; C.N.-P. provided clinical input and interpretation at all stages of the project; all authors were involved in the interpretation of the data, contributed toward critical revision of the manuscript, and approved the final draft; and A.A.S. had full access to all of the data and had final responsibility for the decision to submit for publication.

Conflict-of-interest disclosure: C.N.-P. was codeveloper of the currently available guidelines on VTE prophylaxis in pregnancy issued by the RCOG (green top guideline 37a) and has received honoraria for giving lectures from Leo Pharma and Sanofi-Aventis (makers of tinzaparin and enoxaparin LMWHs used in obstetric thromboprophylaxis) and has received payment from Leo Pharma for development of an educational slide kit about obstetric thromboprophylaxis. The remaining authors declare no competing financial interests.

Correspondence: Matthew J. Grainge, Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Clinical Sciences Building Phase 2, City Hospital, Nottingham, United Kingdom, NG5 1PB; e-mail: matthew.grainge@nottingham.ac.uk.

## References

1. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med.* 2005;143(10):697-706.
2. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol.* 2006;194(5):1311-1315.
3. Lindqvist P, Dahlbäck B, Maršál K. Thrombotic risk during pregnancy: a population study. *Obstet Gynecol.* 1999;94(4):595-599.
4. Martineau M, Nelson-Piercy C. Venous thromboembolic disease and pregnancy. *Postgrad Med J.* 2009;85(1007):489-494.
5. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG.* 2011;118(Suppl 1):1-203.
6. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J; American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6):844S-886S.
7. Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline no. 37a. London, UK: Royal College of Obstetricians and Gynaecologists; 2009.
8. Danilenko-Dixon DR, Heit JA, Silverstein MD, Yawn BP, Petterson TM, Lohse CM, Melton LJ III. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post

partum: a population-based, case-control study. *Am J Obstet Gynecol.* 2001;184(2):104-110.

9. Larsen TB, Sørensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. *Thromb Res.* 2007;120(4):505-509.
10. Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D, Kramer MS; Maternal Health Study Group of the Canadian Perinatal Surveillance System. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can.* 2009; 31(7):611-620.
11. Chan LY, Tam WH, Lau TK. Venous thromboembolism in pregnant Chinese women. *Obstet Gynecol.* 2001;98(3):471-475.
12. Jacobsen AF, Skjeldestad FE, Sandset PM. Ante- and postnatal risk factors of venous thrombosis: a hospital-based case-control study. *J Thromb Haemost.* 2008;6(6):905-912.
13. Knight M; UKOSS. Antenatal pulmonary embolism: risk factors, management and outcomes. *BJOG.* 2008;115(4):453-461.
14. Ros HS, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Pulmonary embolism and stroke in relation to pregnancy: how can high-risk women be identified? *Am J Obstet Gynecol.* 2002;186(2): 198-203.
15. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. *BJOG.* 2001;108(1):56-60.
16. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e691S-736S.
17. The Health Improvement Network. [cited; Available from: http://www.thin-uk.com/
18. Lo Re V III, Haynes K, Forde KA, Localio AR, Schinnar R, Lewis JD. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. *Pharmacoepidemiol Drug Saf.* 2009;18(9): 807-814.
19. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf.* 2007;16(4): 393-401.
20. Green LA. Read Codes: a tool for automated medical records. *J Fam Pract.* 1992;34(5): 633-634.
21. National Institute for Health and Clinical Excellence. Antenatal care: Routine care for the healthy pregnant women. 2008.
22. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. *Br J Clin Pharmacol.* 2000;49(6):591-596.
23. Tata LJ, Hubbard RB, McKeever TM, et al. Fertility rates in women with asthma, eczema, and hay fever: a general population-based cohort study. *Am J Epidemiol.* 2007;165(9):1023-1030.
24. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. *Br J Haematol.* 2012;156(3):366-373.
25. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. *BJOG.* 2008;115(10):1265-1272.
26. Brace V, Kernaghan D, Penney G. Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003-05. *BJOG.* 2007; 114(11):1388-1396.
27. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. *Best Pract Res Clin Obstet Gynaecol.* 2008;22(6):999-1012.
28. Heslehurst N, Ells LJ, Simpson H, Batterham A, Wilkinson J, Summerbell CD. Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. *BJOG.* 2007;114(2):187-194.
29. Office for National Statistics. Birth Statistics: Review of the National Statistician on Births and Patterns of Family Building in England and Wales, 2008: Laid Before Parliament Pursuant to Section 19 Registration Service ACT 1953, Volume 37. London, England: Palgrave Macmillan; 2010.
30. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet.* 2005;365(9461):785-799.
31. Richardson A, Mmata C. *NHS maternity statistics,* England: 2005-06. Leeds, UK: The Information Center; 2007.
32. Royal College of Obstetricians and Gynaecologist. Late intrauterine fetal death and stillbirths Green-top Guideline No.55. London, UK: Royal College of Obstetricians and Gynaecologists; 2010.
33. Office for National Statistics. Ethnicity and national identity in England and Wales 2011. London, England: Office for National Statistics; 2012.
34. Dhalwani NN, Fiaschi L, West J, Tata LJ. Occurrence of fertility problems presenting to primary care: population-level estimates of clinical burden and socioeconomic inequalities across the UK. *Hum Reprod.* 2013;28(4):960-968.
35. Huerta C, Johansson S, Wallander MA, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med.* 2007;167(9):935-943.
36. Själander A, Jansson JH, Bergqvist D, Eriksson H, Carlberg B, Svensson P. Efficacy and safety of anticoagulant prophylaxis to prevent venous thromboembolism in acutely ill medical inpatients: a meta-analysis. *J Intern Med.* 2008;263(1):52-60.
37. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. *J Thromb Haemost.* 2010; 8(5):998-1003.