Impact of risk factors on the timing of first postpartum venous thromboembolism: A population-based cohort study from England

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Abstract

Impact on the timing of first postpartum VTE for women with specific risk factors is of crucial importance when planning the duration of thromboprophylaxis regimen. We observed this using a large linked primary and secondary care database containing 222,334 pregnancies resulting in live and stillbirth births between 1997 and 2010. We assessed the impact of risk factor on the timing on postpartum VTE in term of Absolute rate (AR) and incidence rate ratios (IRR) using Poisson regression model. Of the factors associated with any increased postpartum VTE risk, women with preeclampsia/eclampsia and puerperal infection had the highest risk of VTE in during the first three weeks postpartum (ARs≥2263/100,000 person-years IRR≥2.5) and at 4-6 weeks postpartum (AR≥1360;IRR≥3.5). Women with BMI>30Kg/m^2 or those having caesarean delivery also had elevated rates up to 6 weeks (ARs≥1,425 at 1-3 weeks; and AR≥722 at 4-6 weeks). Women with postpartum haemorrhage or preterm birth, had significantly increased VTE rates only in the first 3 weeks (ARs≥1736, IRR≥2) after which the relative risk became statistically non-significant. Our findings suggests that the duration of the increased VTE risk after childbirth varies based on the type of risk factors and can extend up to the first 3-6 weeks postpartum.

Key points

- Women with preeclampsia, BMI>30Kg/m2, infection or those having caesarean delivery, the VTE risk remained elevated for 6 weeks postpartum.

- For women with postpartum haemorrhage or pre-term birth, the relative rate of VTE was only increased for the first 3 weeks postpartum.

Introduction

Venous thromboembolism (VTE) is a preventable serious maternal complication[1, 2] most likely to occur during the postpartum period.[3-5] Whilst a number of studies[6-9] have identified risk factors for VTE during the postpartum period, there is a lack of evidence quantifying how the impact of risk factors on the incidence of VTE may differ from early to later postpartum periods. The United Kingdom Royal College of Obstetricians and Gynaecologist (RCOG)[10] and the American College of Chest Physician (ACCP)[11] guidelines currently recommend seven days or in-hospital pharmacological postpartum thromboprophylaxis respectively for women with two or more minor risk factors (e.g. smoking, postpartum haemorrhage, pre-eclampsia, caesarean section, obesity) if they have had no previous VTE. These guidelines however are based on expert clinical consensus rather than on robust evidence. Such evidence for the impact on the timing of postpartum VTE for women with specific risk factors is of crucial importance when planning the duration of thromboprophylaxis regimens.[12] Although a large study by Kamel et.al[13] recently looked at the risk of VTE during specific postpartum periods; however they were unable stratify those risk by different risk factors.

Previously our group comprehensively reported the risk factors of VTE during the postpartum period in terms of absolute risks.[14] However, due to the uncertainty of timing of VTE recorded in primary care data, we were then unable to assess the risk of VTE during specific postpartum periods by risk factors. Similarly, previous studies have also failed to report those estimates. Recently linked primary and secondary care data that are representative of the English population provide better information on the timing of VTE than solely using primary care data particularly during the specific postpartum periods.[15] Therefore our aim was to assess the risk of VTE during specific postpartum periods according to women's risk profiles using these prospectively collected primary and secondary

care data. We employed multiple modelling frameworks based on a conceptual hierarchical framework first to such identify risk factors and assess the effects of mutual confounding and mediation by certain risk factors.

Methods

Study population

We used the Clinical Practice Research Datalink (CPRD) [16] which is a large longitudinal UK database that contains computerised primary care (i.e. general practice) records of anonymised patients. Approximately 98% of the England and Wales population are registered with general practitioners (GPs), who are responsible for almost the entirety of a patient's medical care, including coordination of their health care from hospital or other secondary care facilities. The CPRD includes practices who have been trained to record information using the Vision software and who have consented to be included in the database. All patients within a consented practice are automatically included. Around 53% of the CPRD practices are linked to Hospital Episode Statistics (HES)[17] data which contains information on all hospitalisations in England including all discharge diagnoses and procedures. The anonymised patient identifiers from CPRD and HES were linked by a trusted third party using National Health Service (NHS) number, date of birth, postcode and gender.[18] First, patients were matched exactly according to NHS number (over 90% of patients are linked in this way), with the remaining patients linked probabilistically on the basis of postcode, date of birth and gender. As HES only covers English hospitals, practices from Northern Ireland, Wales and Scotland were excluded. Previously data from the linked portion of the CPRD have been shown to be representative in terms of age and sex distribution to data from the UK population published by the Office for National Statistics (ONS). Diagnoses of VTE in primary care[19] and birth information in HES maternity data[20] have been validated to external sources with accuracy with positive predictive values of 84% and 90% respectively. Women aged 15-44 years with HES-recorded pregnancies ending in live birth or stillbirth between 1997 and 2010 and with no VTE before or during pregnancy (as determined from their longitudinal clinical record) were identified within our study population. We therefore had

prospectively recorded health and socio-demographic information for women before and during pregnancy and after delivery.

Defining postpartum venous thromboembolism

We defined first VTE using Read and ICD-10 diagnosis codes for pulmonary embolism or deep vein thrombosis in CPRD and HES respectively (taking the earliest date as the date of diagnosis if the event was recorded in both databases). For VTE events first recorded in HES, the date of VTE was taken as the date of hospital admission. The diagnosis was accepted if supported by one of the following: a prescription of heparin or warfarin within 90 days of diagnosis, evidence of anticoagulant therapy or attendance at an anticoagulant clinic within 90 days of diagnosis, or death within 30 days of diagnosis. Rates of VTE ascertained using this definition have been demonstrated to be highly comparable to incidence rates of VTE in and around pregnancy across other high-income countries and estimation of the date of clinical diagnosis of VTE during specific postpartum periods has been found to be accurate.[15] As 90% of deliveries occurred on the day women were admitted to hospital for delivery or on the day after, the postpartum period was defined from one day before up to 12 weeks post-delivery. This was to ensure complete capture of all pregnancy-related VTE diagnosed during the postpartum period.

Defining potential risk factors

Demographics, lifestyle characteristics and pre-existing co-morbidities

For all pregnancies we extracted information on women's demographic and lifestyle characteristics as well as important co-morbidities from both primary and secondary care data. Information on body mass index (BMI) (Kg/m^2), cigarette smoking (current, ex-smoker or non-smoker), ethnicity (white or non-white) and age at delivery were obtained from CPRD data, whilst cardiac disease, varicose veins, inflammatory bowel disease (IBD), pre-existing

diabetes and hypertension were ascertained using both CPRD and HES using methods similar to previously described using primary care data.[14] Similarly we defined women as having pre-existing renal disease if they had a diagnosis of acute or chronic kidney disease, glomerular or renal tubule-interstitial disease before conception in HES or CPRD.

Pregnancy characteristics and complications

Pre-eclampsia/eclampsia, hyperemesis, multiple birth, gestational diabetes or hypertension as previously defined[14] were extracted using both CPRD and HES. We also investigated two common acute systemic infections during pregnancy (urinary and respiratory tract (pneumonia, acute bronchitis, chest infection and influenza)) as these have been associated with VTE in non-pregnant populations.[21, 22]

Delivery characteristics and complications

From HES we extracted risk factors occurring around delivery: length of gestation, mode of delivery (spontaneous, assisted (forceps, breech or vacuum), emergency or elective caesarean), stillbirth, and postpartum haemorrhage (including intra-partum haemorrhage). We also investigated acute systemic infections during the postpartum period, termed puerperal infection.

Statistical analysis

We calculated incidence rates of VTE per 100,000 person-years and 95% confidence intervals by dividing the number of VTEs by the postpartum follow-up time, stratified by each demographic and lifestyle characteristic, pre-existing co-morbidity, pregnancy and delivery characteristic and complication. Using Poisson regression we calculated unadjusted incidence rate ratios (IRR) for the associations between each risk factor and VTE. We fitted a clustering term to take into account multiple pregnancies experienced by an individual

woman over the study period. For associations where the likelihood ratio (LRT) test p-value was <0.1 we included these risk factors in multivariate models that were constructed using a pre-developed conceptual hierarchical framework (Figure 1) as a tool to assess the complex causal pathways between variables.[23] For instance, some of the impact of delivery complications (e.g. mode of delivery, postpartum haemorrhage) on postpartum VTE may be confounded by pregnancy characteristics (e.g. pre-eclampsia), pre-existing medical co-morbidities (e.g. cardiac disease) or demographic factors (e.g. maternal age), however each of these factors may also have direct effects on postpartum VTE that are not mediated through delivery complications.

In our hierarchical framework we grouped factors that were considered to have more proximate associations with postpartum VTE (e.g. caesarean section) separately from more distant factors (e.g. pre-pregnancy BMI) that may have direct effects on VTE but may also have indirect effects mediated through proximate risk factors (e.g. pre-pregnancy BMI is related to one's likelihood of developing pre-eclampsia, the latter being a more proximate risk factor for VTE).[24] Based on this we created three modelling frameworks (MF) to present rate ratio estimates adjusted for different groups of risk factors. In modelling framework 1 we created separate models for each pre-existing co-morbidity, pregnancy and delivery characteristic/complication to estimate their overall effects on postpartum VTE, adjusting only for demographic and lifestyle characteristics (maternal age, BMI, cigarette smoker). In MF 2, models from MF 1 were additionally adjusted for any pre-existing medical co-morbidities (e.g. cardiac disease). In MF 3, models were adjusted for demographic and life style related factors, pre-existing medical co-morbidities and pregnancy related characteristics and complications, to estimate each of their effects unmediated by their more proximate risk factors, and also the fully adjusted effects of each delivery characteristic/complication. At that point we re-added statistically non-significant variables

previously excluded to assess if they became significant. Because the direction of causal pathways between caesarean delivery and other delivery complications (e.g. stillbirth) can vary, we carried out a subgroup analysis restricting to women who only underwent spontaneous vaginal or assisted delivery.

For pregnancy and delivery complications showing increased postpartum VTE risks with more than 10 associated VTE events (to ensure reasonable precision), we assessed whether the absolute and relative risks (AR and RR) of VTE differed during the early postpartum (weeks 1-3 and weeks 4-6 post-delivery) and late postpartum (weeks 7-12 post-delivery). For the purpose of this analysis we also evaluated the risk of VTE within the one year after the 12 weeks postpartum period (one year from 13th weeks). Although the rate of VTE expressed as per 100,000 person-years during postpartum periods helps in standardization and comparison of the estimates, we also calculated the rate of VTE per 100,000 pregnancies which are of clinical value. We used those estimates to calculate the Number Needed to Treat (NNT) to prevent one VTE assuming that thromboprophylaxis reduces the VTE risk by 50% based on the randomised trials of general medical patients.[25] We also calculated the NNT based on the 88% risk reduction observed among non-randomised pregnant women.[26]

For our sensitivity analysis, we re-ran all models, excluding a small proportion (7%) of VTE events first recorded in HES because they occurred during the same hospital admission as the delivery or another risk factor event (e.g. postpartum haemorrhage) and therefore precise temporality could not be established (i.e. we could not determine whether VTE was the cause or consequence of a caesarean section or postpartum haemorrhage, particularly for those occurring on the same day).

Ethical statement

This study was approved by the Independent Scientific Advisory Committee (ISAC) reference number=10_193R.

Results

Among 168,077 women there were 222,334 pregnancies ending in live birth or stillbirth. There were a total of 178 VTE events which occurred during the postpartum period. Table 1 shows absolute rates of postpartum VTE and associations with each of the 21 risk factors assessed, 14 of which were significantly associated with postpartum VTE in bivariate models (LRT $p<0.01$).

Multivariate analyses of postpartum VTE risks

When we assessed the direct and mediated effects of each factor using different modelling frameworks (Figure 1 and Table 2), we found that high BMI was associated with increased postpartum VTE risk across all three models indicating that little of the obesity-associated risk was mediated through other factors, pre-existing, or pregnancy related. Similarly there were almost 4-fold and 3-fold increased risks for women previously diagnosed with varicose veins and cardiac disease respectively, which did not appear to be strongly mediated by other risk factors. For delivery characteristics and complications we found a 7-fold (95%CI 3.33-15.4) increased risk of VTE for those with stillbirth even after adjusting for important background factors. Elective caesarean and emergency caesarean, puerperal infection and pre-term birth were associated with at least 2-fold increased risks compared to spontaneous vaginal deliveries, those with no puerperal infection, with normal gestational length respectively. These factors were still important even after adjusting for women's pre-existing co-morbidities and factors occurring prior delivery. The increased risk of VTE observed with BMI $\geq$30 Kg/m^2 and caesarean section remained consistent when we restricted our analysis to women without any other risk factor (Supplementary table 1).

Even among women with spontaneous vaginal deliveries, stillbirth, postpartum haemorrhage, puerperal infection, pre-term birth, pre-eclampsia/eclampsia, varicose veins and BMI≥30Kg/m^2 were still associated with increased risks (Table 2). No associations changed when we excluded the 7% of VTE events occurring during the same hospital admission as the delivery or risk factor event where we could not establish their relative order.

Variation in VTE incidence and incidence rate ratios during postpartum periods

When we ascertained absolute risks of VTE within specific postpartum intervals (Table 3), we found that women with preeclampsia/eclampsia and puerperal infection had the highest risk of VTE in during the first three weeks postpartum (AR=2263 and AR=4813 per 100,000 person-years respective). The risk also remained elevated in the 4-6 weeks postpartum for those risk factors, although to a lesser extent (AR>890 per 100,000 person-years). Women with BMI>30Kg/m^2 or those who had caesarean delivery, also had elevated rate of VTE up to 6 weeks postpartum (ARs>1,400/100,000 person-years in weeks 1-3 and >700 in weeks 4-6). However for women with postpartum haemorrhage or pre-term birth, the relative rate of VTE was only increased for the first 3 weeks postpartum (ARs=1-2/100 person-years). Within a year after the 12 weeks postpartum (Figure 2) the absolute rate of VTE associated with those risk factors became similar to that of non-pregnant women of childbearing age (30/100,000 person-year). Our absolute rates of VTE for the above stated risk factors were broadly similar when restricted to the first week compared to those over weeks 1-3 postpartum (Supplemental table 2).

Number needed to treat during weeks of postpartum

Table 4 contains the risk of VTE per 100,000 pregnancies and NNT for each specific risk factor. Based on a 50% risk reduction we observed that during the first three weeks of postpartum, the lowest NNT was 1,173 for women with puerperal infection, followed by

women with pre-eclampsia/eclampsia (NNT=1,289). The NNT values were all around 1,600 for women preterm births, postpartum haemorrhage or BMI>30Kg/m^2. At 4-6 weeks postpartum, the lowest NNT was for women with pre-eclampsia/eclampsia (NNT=2,557) followed by BMI>30Kg/m^2 (NNT=4,734) and caesarean section (NNT=4,816).

Discussion

Main findings

This study provides precise absolute and relative risks of postpartum VTE for maternal risk factors occurring before, during and after childbirth and quantifies which have the greatest impact on VTE during specific postpartum intervals. We found that women with stillbirths, per-term birth, postpartum haemorrhage, puerperal infection, caesarean delivery and high BMI (>30Kg/m^2) were at a high risk of postpartum VTE. The augmented risks associated with these factors were not explained by other pregnancy characteristics and complications, pre-existing co-morbidities, demographics or lifestyle factors considered in this study. We found that for women with preeclampsia/eclampsia, BMI>30Kg/m2, puerperal infection or those having caesarean delivery, the rate of VTE remained elevated for 6 weeks postpartum. However for women with postpartum haemorrhage or pre-term birth, the relative rate of VTE was only increased for the first 3 weeks postpartum with NNTs of 933 and 956 respectively.

Strengths and weaknesses

Our study used information on more than 222,000 pregnancies with postpartum follow-up using linked primary and secondary care data which covers 3% of the UK population and has similar age and sex distribution to the national population. Our study findings are therefore reasonably generalisable to pregnant women in England with no prior diagnosis of VTE and to women in other high-income countries with similar health care systems. By using linked primary and secondary care data we had comprehensive medical information on women's baseline health risks recorded before pregnancy as well as their pregnancy and delivery health records, all of which were prospectively recorded. This enabled us not only to assess the impact of risk factors on postpartum VTE while adequately controlling for confounding factors but also to assess the impact of risk factors on the incidence of VTE during specific postpartum periods.

Another strength of this study was our use of a conceptual hierarchical framework to adjust our estimates for potential confounding factors. Most previous studies have used stepwise regression models for their risk factor analysis. This is solely reliant on statistical association rather than any conceptual basis for the interrelationship between factors where all explanatory variables are treated at the same hierarchical level, an assumption which may not be appropriate in all cases particularly for closely related factors around pregnancy and delivery. In contrast our categorisation of risk factors and adjustments in hierarchical order enabled us to better evaluate the extent to which the effect of a particular risk factor had a direct effect or was mediated by other risk factors. (e.g. whether the effect of stillbirth is mediated by more distant risk factors such as age and/or BMI).

A limitation of this analysis is our inability to establish temporality between VTE and risk factors that were recorded during the same hospital admission as the VTE event (e.g. postpartum haemorrhage). However this only affected 7% of our cases and our sensitivity analysis demonstrated that removing those women from our analysis did not affect our estimates. We also acknowledge that we were not able to consider certain risk factors such as family history of VTE and thrombophilia. However we believe that the following arguments should be considered. Firstly, whilst family history may be important, it has rarely been looked at in previous population-based studies, possibly for the reason that accurate recall of a family history is problematic. Secondly thrombophilia screening is not routinely recommended for pregnant women therefore pragmatically it cannot be used as a predictor for VTE outcome.

The hospital and general practice data used in our study is directly from routinely implemented clinical practice provided by the UK National Health Service which is free at

the point of access, and whilst VTE has been validated with reasonably accuracy,[15, 19] there is a lack of validation studies on medical codes for pregnancy-related risk factors such as pre-eclampsia, postpartum haemorrhage. However a systematic review of overall discharge diagnosis coding in HES has demonstrated high accuracy (91%). Whilst there are a very limited number of studies estimating the population-based prevalence of pregnancy-related illnesses, the prevalence of hypertension, pre-eclampsia, diabetes, caesarean section, stillbirths, postpartum haemorrhage and preterm births in our population were very similar to the available evidence from national or other similarly developed countries.[27-33]

We would also like to highlight that, because prescriptions are available from general practice but not from hospital data,[15] our estimates do not take into account that certain women may have been receiving thromboprophylaxis during the risk periods assessed, which may have led to an underestimation of risk. However, we believe that since the first RCOG guidelines for postnatal thromboprophylaxis were only published in 2004 (updated 2009), the use of thromboprophylaxis with LMWH was unusual before 2004 except for those women with previous VTE. There is also evidence suggesting the underuse of prophylaxis among post caesarean section women.[34] Additionally, 67% of all pregnant women diagnosed with antepartum pulmonary embolism (between 2005 and 2006) in the UK did not receive pharmacological thromboprophylaxis according to national guidelines even though they qualified for thromboprophylaxis[35] so we do not believe this would have resulted in substantial underestimation.

Finally we acknowledge that some of the numbers in our postpartum analysis are small which could lead to type 2 error. However a large study conducted by Kamel et al[13](which utilised information on 1.6 million pregnancies but did not assess risk factors) showed an overall

elevated risk of thrombosis which persisted until at least 12 weeks after delivery. This might be due to certain risk factors which we have highlighted in our study.

Comparison with other literature

Our relative increased risks observed for women with BMI≥30Kg/m^2, cardiac disease, varicose veins, pre-eclampsia/eclampsia and puerperal infection are in concordance with most previous studies.[6, 7, 9, 36-38] Additionally our study findings support increased risks of more than 2-fold and 6-fold in women experiencing pre-term delivery and stillbirth respectively, both of which have been previously reported.[9, 14, 37] We also found a 2-fold relative increase in the risk of VTE for both elective and emergency caesarean delivery compared to spontaneous vaginal delivery. Our finding of an increased risk of VTE associated with elective caesarean section contradicts that of Jacobsen et al[36] who only found an increased VTE risk associated with emergency caesarean section. Jacobsen et al[36], however, obtained VTE cases using a patient registry for the whole population of Norway and controls from a single hospital where they had many more elective caesarean sections (9.2%) compared to the general population (4.8%), which may have biased their estimates towards null. Similarly to previous studies, we were not able to look at the reasons for caesarean section in more detail, for example the urgency grade of the caesarean section[39] as clinical classification of emergency and elective caesarean section in practice remains crude.

We found only one published study evaluating the impact of multiple risk factors on the absolute and relative rates of VTE in different specific postpartum periods. Morris et al[37] in a population-based study from Australia showed that a high absolute rate of pulmonary embolism (PE) persists for up to 4 weeks after caesarean delivery. This may have been underestimated as only secondary care data were used to identify PE cases and hospital admission date was considered as the date of diagnosis. The higher relative risk of VTE that

we found associated with obesity and caesarean delivery in weeks 4-6 following delivery than in the first three weeks may be explained by the fact that those women would have received some form of thromboprophylaxis during the initial postpartum week, as suggested by the current thromboprophylaxis guidelines, which we were not able to quantify. However there was no overall statistical difference in the rate of VTE among those with caesarean section or BMI≥30Kg/m^2 when we assessed this before and after 2004.

We were also not able to calculate the absolute rate of VTE during the specific postpartum periods among those with stillbirths due to insufficient power. However 75% (n=6) of VTE cases occurred during the first 3 weeks postpartum which highlights the importance of VTE risk assessment during that period. Finally our calculated NNTs during those periods should be interpreted with caution as they are based on non-trial data regarding the reduction in risk after low molecular weight heparin in non-pregnant populations.

Clinical implication

Our results have important implications for deciding how and when thromboprophylaxis is delivered in the obstetric health care setting and will help targeting of thromboprophylaxis in the following ways; Firstly, our results suggest that the increased risk of VTE extends beyond the currently suggested 7 days for women with certain risk factors. Secondly we found that for women with preeclampsia/eclampsia, BMI>30Kg/m2, puerperal infection or those having caesarean delivery, the rate of VTE remained elevated for 6 weeks postpartum. However for women with postpartum haemorrhage or pre-term birth, the relative rate of VTE was only increased for the first 3 weeks postpartum with a NNT of 1739. This suggests that the time period of increased risk of VTE during the postpartum is dependent on the type of risk factors which should be considered when planning thromboprophylaxis. Finally, women whose pregnancies are complicated by stillbirth, high BMI, pre-term birth, caesarean section,

puerperal infection or postpartum haemorrhage should be considered at high risk (AR=0.6-2.5 per 100 person-years) of VTE postnatally. The augmented risks associated with these factors are not explained by other pregnancy characteristics and complications, pre-existing co-morbidities, demographics or lifestyle factors. Therefore pregnancies complicated by any one of those factors may require careful consideration in terms of VTE risk assessment during the immediate postpartum.

Recommendations regarding postpartum thromboprophylaxis with low molecular weight heparin for women with the above highlighted risk factors will of course be highly dependent on the risk reduction from prophylaxis and any adverse events from its use. Nevertheless our study provides the most robust, comprehensive and clinically relevant information on risk factors for postpartum VTE that can be of direct use in formulating such guidelines.

Acknowledgements

Competing interest statement

CNP was co-developer of the currently available guidelines on VTE prophylaxis in pregnancy issued by the Royal College of Obstetricians and Gynaecologists (green top guideline 37a). CNP has also 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. No other authors have conflicts of interest to declare.

Details of Contributions

AAS, LJT, JW and MJG conceived the idea for the study, with KMF also making important contributions to the design of the study. AAS carried out the data management and analysis and wrote the first draft of the manuscript. CNP provided clinical input and interpretation at all stages of the project. All authors were involved in the interpretation of the data, contributed towards critical revision of the manuscript and approved the final draft. AAS had full access to all of the data and AAS and LJT had final responsibility for the decision to submit for publication.

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Table 1: Incidence rates of postpartum VTE per 100,000 person-years and IRRs for potential delivery, pregnancy and pre-existing risk factors (222,334 pregnancies)

Variable	Pregnancies N (%) Total=222,334	Postpartum VTE N Total=178	Rate(95%CI)*	IRR (95%CI) Unadjusted
Demographic and lifestyle characteristics				
Maternal age at delivery				
15 – 19 years	12,927 (5.8)	5	170 (70-408)	0.43 (0.17-1.08)
20 – 24 years	36,960 (16.6)	28	330 (228-478)	0.84 (0.53-1.33)
25 - 29 years	58,207 (26.1)	53	390 (298-551)	1.00
30 – 34 years	68,753 (30.9)	37	228 (165-315)	0.58 (0.38-8.90)
35 – 39 years	37,968 (17.0)	44	491 (366-661)	1.25 (0.84-1.87)
40 – 44 years	7,519 (3.3)	11	325 (346-1130)	1.60 (0.83-3.06)
Body mass index (Kg/m^2)				
Normal(18.5-24.9)	98,730 (44.4)	60	259 (201-334)	1.00
Underweight(<18.5)	7,339 (3.30)	3	179 (56-545)	0.67 (0.21-2.16)
Overweight(25-29.9)	39,652 (17.8)	33	353 (252-499)	1.36 (0.89-2.09)
Obese(30-40)	21,410 (9.6)	28	558 (385-808)	2.14 (1.37-3.36)
Class 3 obese (>40)	2,731 (1.2)	12	1881 (1068-3312)	7.24 (3.89-13.4)
Ethnicity				
White	159,159 (71.5)	129	347 (292-412)	1.00
Non white	21,178 (9.5)	21	430 (280-658)	1.23 (0.78-1.96)
Missing	41,997 (18.8)	28	284 (196-411)	0.81 (0.54-1.23)
Cigarette smoker	51,731 (23.2)	51	424 (322-558)	1.24 (0.88-1.76)
Ex-smoker	55,743 (25)	36	275 (198-382)	0.81 (0.55-1.19)
Pre-existing co-morbidities				
Varicose veins	5,895 (2.65)	16	1154 (707-1884)	3.59 (2.15-6.01)
Cardiac disease	2,264 (1.0)	5	945 (393-2271)	2.80 (1.15-6.83))
Inflammatory bowel disease	1,105 (0.5)	4	1545 (580-4117)	4.58 (1.69-12.3)
Pre-existing hypertension	13,814 (6.5)	17	524 (326-844)	1.68 (1.01-2.78)
Pre-existing diabetes	2,501 (1.1)	4	685 (257-1826)	2.03 (0.75-5.46)
Pre-existing renal disease	1,493 (0.7)	2	575 (143-2300)	1.68 (0.41-6.78)
Pregnancy characteristics and complications				
Antepartum haemorrhage	10,329 (4.6)	10	416 (224-774)	1.22 (0.64-2.31)
Acute systemic infection	26,572 (11.9)	20	323 (208-550)	0.93 (0.58-1.48)
Pre-eclampsia/eclampsia	5,237 (2.3)	14	1148 (679-1938)	3.54 (2.05-6.11)
Multiple birth	3,282 (1.4)	3	390 (125-1211)	1.14 (0.36-3.57)
Gestational hypertension	11,796 (5.6)	18	655 (413-1041)	2.10 (1.28-3.43)
Gestational diabetes	3,518 (1.6)	4	486 (182-1294)	1.44 (0.53-3.88)
Hyperemesis	7,838 (3.53)	9	494 (257-950)	1.46 (0.74-2.86)
Delivery characteristics and complications				
Length of gestation				
Normal gestation	184,744 (83.0)	15	313 (264-370)	1.00
Pre-term gestation	17,112 (7.7)	29	727 (505-1047)	2.31 (1.55-3.46)
Prolonged gestation	20,478 (9.2)	14	293 (173-494)	0.93 (0.53-1.62)
Mode of delivery				
Spontaneous	141,1207 (63.5)	76	230 (184-288)	1.00
Assisted	26,943 (12.1)	19	304 (194-476)	1.31 (0.79-2.18)
Elective caesarean	22,341 (10.0)	33	630 (448-886)	2.73 (1.81-4.11)
Emergency caesarean	31,843 (14.3)	50	674 (511-890)	2.92 (2.04-4.18)
Stillbirth	1,356 (0.61)	8	2595 (1297-5189)	7.86 (3.87-15.9)
Postpartum haemorrhage	20,762 (9.34)	30	629 (440-900)	2.00 (1.35-2.96)
Puerperal infection	7,740 (3.4)	18	1291 (813-2049)	4.07 (2.50-6.63)

*Rate calculated per 100,000 person-years. IRR: Incidence rate ratio CI: confidence interval

Table 2: Multivariate analysis for VTE risk factors during the postpartum period

Variable	Incidence rate ratios (95%CI)			
	Modelling framework 1	Modelling framework 2	Modelling framework 3	Modelling framework 3 restricted to Spontaneous vaginal/Assisted deliveries
Demographic and lifestyle characteristics				
Maternal age at delivery				
Age (for every years increase)[◊]	1.03 (1.00-1.06)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (0.98-1.07)
Body mass index (Kg/m^2)				
Normal(18.5-24.9)	1.00	1.00	1.00	1.00
Underweight(<18.5)	0.70 (0.21-2.27)	0.69 (0.21-2.23)	0.74 (0.23-2.39)	0.84 (0.19-3.56)
Overweight(25-29.9)	1.35 (0.88-2.07)	1.36 (0.89-2.09)	1.21 (0.77-1.90)	0.67 (0.30-1.46)
Obese(30-40)	2.13 (1.36-3.34)	2.15 (1.37-3.37)	1.91 (1.18-3.11)	2.57 (1.37-4.82)
Class 3 Obese(≥40)	7.23 (3.89-13.4)	7.45 (4.00-13.8)	6.36 (3.19-12.6)	11.5 (4.96-26.6)
Cigarette smoker	1.43 (1.03-1.99)	1.44 (1.04-2.00)	1.38 (0.97-1.96)	1.16 (0.71-1.89)
Pre-existing co-morbidities				
Varicose veins	3.50 (2.09-5.87)	3.50 (2.09-5.78)	3.97 (2.36-6.68)	4.88 (2.61-9.11)
Cardiac disease	2.67 (1.09-6.53)	2.59 (1.05-6.33)	2.78 (1.02-7.53)	2.69 (0.66-10.9)
Inflammatory bowel disease	4.59 (1.69-12.4)	4.61 (1.70-12.4)	2.62 (0.64-10.6)	**
Pre-existing hypertension	1.46 (0.88-2.43)	-	-	-
Pregnancy characteristics and complications				
Pre-eclampsia/eclampsia	3.31 (1.78-6.43)	3.18 (1.81-5.72)	4.41 (1.29-15.0)	3.02 (1.20-7.61)
Gestational hypertension	1.83 (1.10-3.04)	1.86 (1.12-3.08)	0.78 (0.26-2.33)	-
Delivery characteristics and complications				
Pregnancy length				
Normal gestation (37-42 weeks)	1.00	1.00	1.00	1.00
Pre-term gestation (<37 weeks)	2.25 (1.50-3.38)	2.27 (1.51-3.40)	2.09 (1.39-3.13)[1]	1.90 (1.05-3.44)
Pro-longed gestation (>42 weeks)	0.90 (0.52-1.57)	0.91 (0.57-1.57)	0.89 (0.49-1.60)[1]	1.02 (0.49-2.11)
Mode of delivery				
Spontaneous	1.00	1.00	1.00	-
Assisted delivery	1.38 (0.83-2.28)	1.41 (0.85-2.34)	1.29 (0.76-2.20)[2]	-
Elective caesarean delivery	2.39 (1.55-3.68)	2.39 (1.55-3.69)	2.47 (1.58-3.85)[2]	-
Emergency caesarean delivery	2.78 (1.93-4.01)	2.81 (1.95-4.05)	2.23 (1.50-3.33)[2]	-
Stillbirth outcome	7.42 (3.64-15.1)	7.57 (3.71-15.4)	7.17 (3.33-15.4)	11.9 (5.43-26.1)
Postpartum haemorrhage	1.93 (1.30-2.87)	1.93 (1.30-2.86)	1.78 (1.17-2.72)	2.35 (1.32-4.17)
Puerperal infection	4.18 (2.72-6.43)	4.07 (2.64-6.28)	3.72 (2.32-5.97)	3.59 (1.85-6.96)

Modelling framework (MF) 1: Models are built for each risk factor separately, adjusting for demographic and lifestyle characteristics only

Modelling framework 2: As MF 1 and additionally adjusted for pre-existing co-morbidities

Modelling framework 3: As MF 2 and additionally adjusted for pregnancy characteristics and complications

**No VTE events to perform analysis

[1] Additionally adjusted for stillbirths

[2] Additionally adjusted for stillbirths, puerperal infection and postpartum haemorrhage

[◊]Age taken as a continuous variable.

Table 3: Incidence rates of VTE per 100,000 person-years and IRRs during different periods of postpartum and around delivery

	1-3 weeks postpartum			4-6 weeks postpartum			7-12 weeks postpartum		
	VTE	**Rate (95%CI)[2]**	**IRR (95%CI)[1]**	**VTE**	**Rate(95%CI)[2]**	**IRR (95%CI)[1]**	**VTE**	**Rate(95%CI)[2]**	**IRR (95%CI)[1]**
BMI≥30Kg/m²									
No	40	598 (438-815)	1.00	9	161 (84-311)	1.00	11	101 (56-182)	1.00
Yes	27	1650 (1131-2406)	2.74 (1.66-4.52)	10	735 (395-1366)	4.18 (1.65-10.5)	3	112 (36-350)	0.97 (0.4-3.88)
Preeclampsia/eclampsia									
No	119	814 (680-974)	1.00	27	221 (151-322)	1.00	18	75 (47-119)	1.00
Yes	8	2263 (1131-4525)	2.54 (1.23-5.26)	4	1360 (510-3623)	5.41 (1.84-15.8)	2	349 (87-1397)	4.76 (1.05-21.6)
Length of gestation									
Normal (36-42 weeks)	98	788 (646-960)	1.00	22	211 (139-321)	1.00	15	73 (44-122)	1.00
Pre-term (<37 weeks)	20	1736 (1120-2691)	2.04 (1.26-3.28)	5	519 (216-1247)	1.92 (0.77-4.78)	4	213 (80-569)	2.81 (0.86-9.16)
Caesarean section									
No	75	662 (528-831)	1.00	9	95 (49-182)	1.00	11	59 (33-107)	1.00
Yes	52	1425 (1086-1870)	1.89 (1.30-2.74)	22	722 (475-1096)	6.99 (3.07-15.9)	9	151 (78-290)	2.22 (0.85-5.79)
Postpartum haemorrhage									
No	103	756 (623-917)	1.00	27	237 (163-346)	1.00	18	81 (51-129)	1.00
Yes	24	1778 (1192-2653)	2.22 (1.42-3.47)	4	347 (130-353)	1.38 (0.47-4.04)	2	88 (22-353)	1.00 (0.22-4.46)
Puerperal infection									
No	114	775 (645-932)	1.00	28	230 (158-333)	1.00	18	76 (48-121)	1.00
Yes	13	4813 (279-828)	5.99 (3.36-10.6)	3	899 (289-2787)	3.56 (1.08-11.7)	2	253 (63-1011)	3.27 (0.73-14.6)

[1]Adjusted for demographic characteristics, pre-existing medical co-morbidities and pregnancy related complication and characteristics when not stratified by them

[2]Rate per 100,000 person-years

IRR: Incidence rate ratio

CI: confidence interval

Table 4: Absolute rate of VTE per 100,000 pregnancies and number needed to treat (NNT)

Risk factors	1-3 weeks postpartum	4-6weeks postpartum	7-12 weeks postpartum
BMI≥30Kg/m²			
Rate (95%CI)	113 (74-164)	42 (20-77)	13 (2-37)
NNT (50% risk reduction)	1,771	4,734	15,398
NNT (88% risk reduction)	1,006	2,690	8,749
Preeclampsia/eclampsia			
Rate (95%CI)	155 (67-305)	78 (21-200)	40 (48-145)
NNT (50% risk reduction)	1,289	2,557	4,974
NNT (88% risk reduction)	733	1,453	2,826
Per-term birth			
Rate (95%CI)	119 (73-183)	30 (9-69)	24 (6-62)
NNT (50% risk reduction)	1,683	6,700	8,249
NNT(88% risk reduction)	956	3,807	4,687
Caesarean section			
Rate (95%CI)	98 (72-127)	42 (26-63)	17 (7-33)
NNT (50% risk reduction)	2050	4816	11502
NNT (88% risk reduction)	1,165	2,737	6,535
Postpartum haemorrhage			
Rate (95%CI)	122 (78-181)	20 (5-51)	10.2 (1-36)
NNT (50% risk reduction)	1,642	10,018	19,689
NNT (88% risk reduction)	933	5,692	11,187
Puerperal infection			
Rate (95%CI)	249 (15-38)	39 (8-114)	27 (3-96)
NNT (50% risk reduction)	1173	5,090	7,479
NNT (88% risk reduction)	667	2,892	4,249

NOTE: Absolute rates per 100,000 are based on the number of pregnancies complicated by a particular risk factor (Table 1) divided by VTE events.
It does not consider postpartum haemorrhage, puerperal infections as time varying covariates nor censor postpartum follow-up time after a VTE event.

Figure legends

Figure 1: Conceptual hierarchical framework for multivariate modelling of risk factors for VTE during the postpartum period

Figure 2: Absolute rate of VTE in the postpartum period by risk factors.

Figure 1: Conceptual hierarchical framework for multivariate modelling of risk factors for VTE during the postpartum period

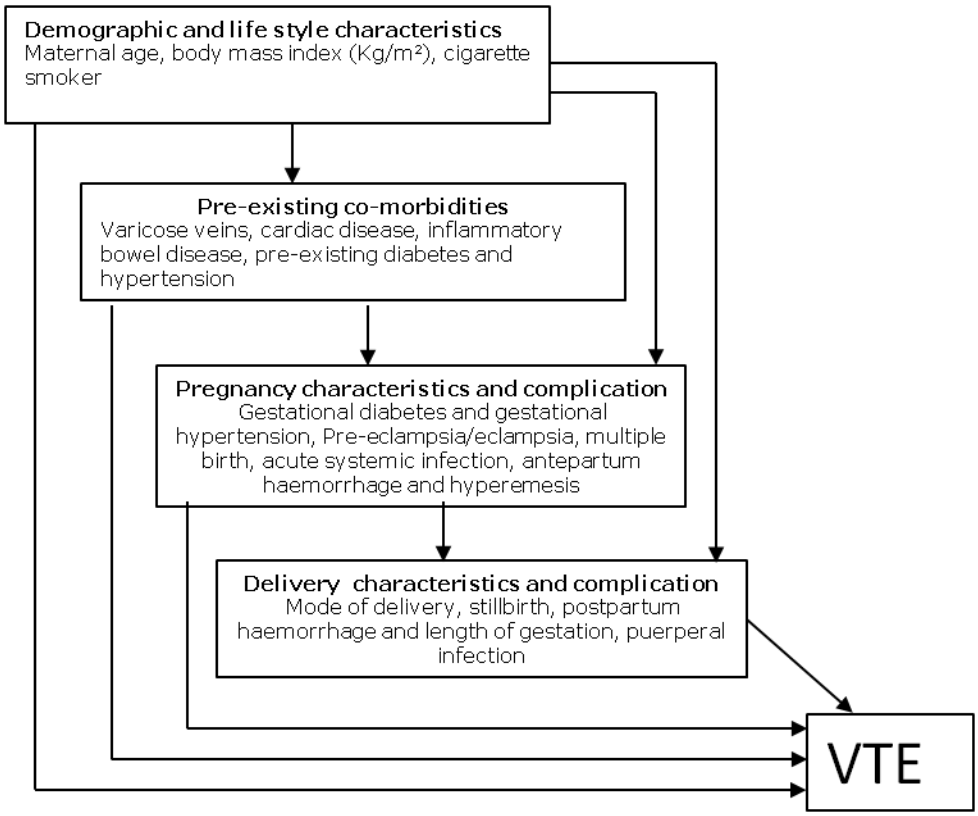
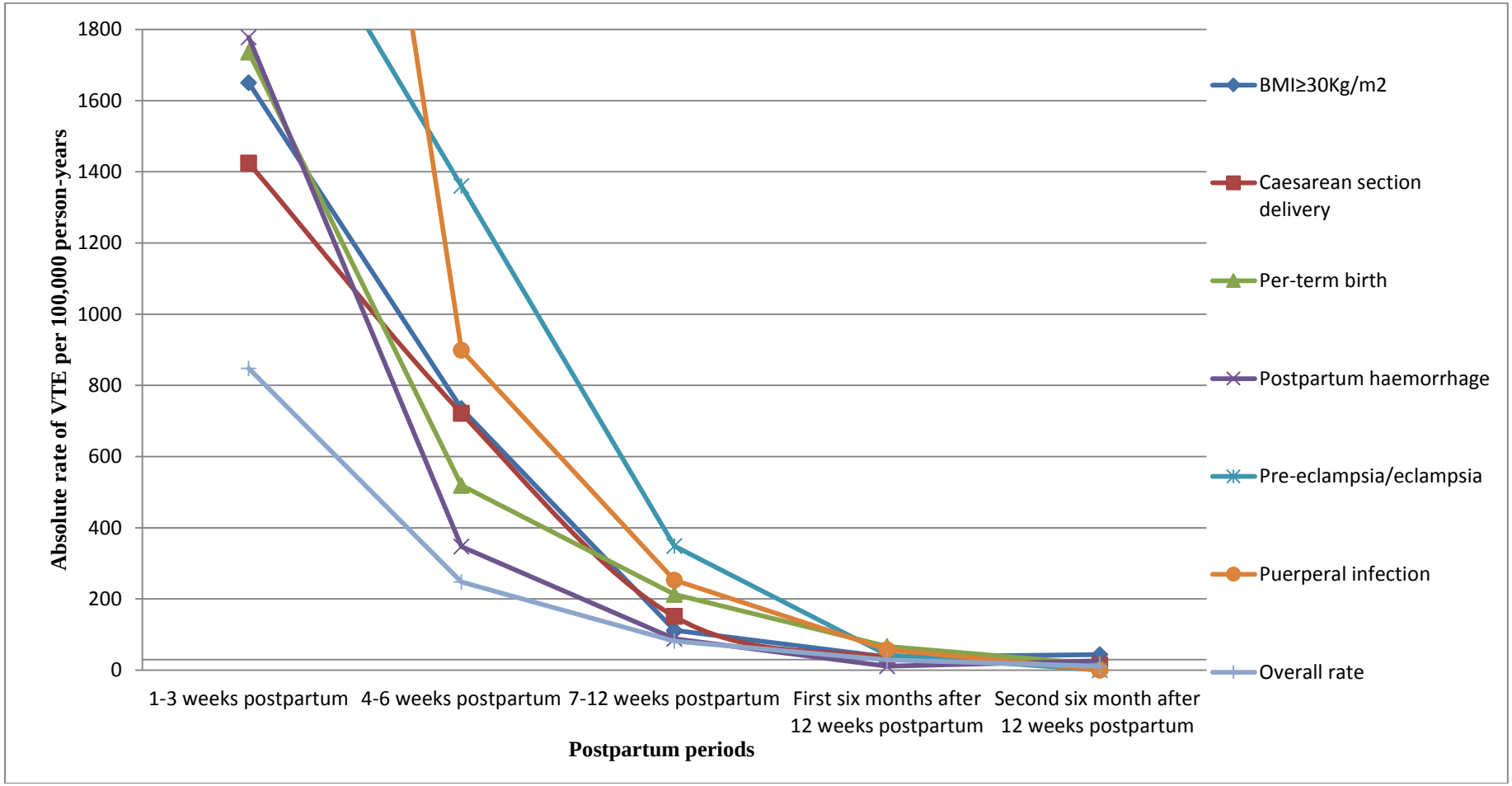


Figure 2: Absolute rate of VTE in the postpartum period by risk factors.



Abbreviations:

AR = Absolute Rate

BMI = Body Mass Index

CPRD = Clinical Practice Research Datalink

HES = Hospital Episode Statistics

IBD = Inflammatory Bowel Disease

IRR = Incidence Rate Ratio

NNT = Number Needed to Treat

RCOG = Royal College of Obstetricians and Gynaecologists

ACCP = American College of Chest Physician