VTE Risk Assessment and Prevention in Pregnancy

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Abstract

Venous thromboembolism (VTE) remains the leading cause of maternal mortality in pregnancy and the postpartum period. In addition to the higher pregnancy-associated baseline VTE risk, there are several well-established risk factors that can further increase the risk of VTE. At present, a thorough interrogation of these risk factors remains our only tool for estimating which pregnant people may be at an increased risk of VTE, and thus potentially benefit from thromboprophylaxis. However, an important knowledge gap still exists surrounding the duration of increased risk and the interaction of risk factors with each other. Furthermore, up to now, once significant risk has been established, prevention strategies have been largely based on expert opinion rather than high-quality data. Recent trials have successfully bridged a proportion of this knowledge gap; however, the challenge of conducting high-quality clinical trials with pregnant people remains. In this article, we provide an update on the recent evidence surrounding VTE risk factors in pregnancy while concurrently outlining knowledge gaps and current approaches to VTE prevention.

Keywords
- venous thromboembolism
- pregnancy
- risk assessment

Introduction

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). Despite improvements in care pathways for pregnant people, VTE is still a leading cause of death in pregnancy and in the postpartum period.[1] During 2014 to 2016, VTE was listed as the leading cause of direct maternal death (defined as death from a cause arising directly from pregnancy) in the United Kingdom and Ireland, at 1.39 (95% confidence interval [CI]: 0.95–1.96) per 100,000 pregnancies.[2] A maternal death due to PE has tragic and wide-reaching consequences for the mother's family, friends, and society. VTE can also result in lifelong physical and psychological impairment.[3]

VTE risk increases during pregnancy and reaches a peak in the early postpartum period. The pooled incidence rate of VTE in a systematic review restricted to studies in which VTE cases were validated was reported to be 118 (95% CI: 101–137) per 100,000 person-years during the antepartum period and 424 (95% CI: 238–755) per 100,000 person-years during the postpartum period.[4] Superficial venous thrombosis (SVT) is also common during pregnancy and postpartum and, while it is a manifestation of VTE, is also a strong risk factor for pregnancy-associated DVT. A nationwide cohort study including data from Danish registries was published recently.[5] Among 1,276,046 deliveries, 710 diagnoses of lower extremity SVT were reported during pregnancy and up to 12 weeks postpartum (0.6 per 1,000 person-years [95% CI: 0.5–0.6]). Among 211

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people with and without antepartum SVT, 22 (10.4%) and 25 (11.8%), respectively, were diagnosed with DVT (hazard ratio [HR]: 83.3 [95% CI: 46.3–149.7]).

What causes this pregnancy-related increase in VTE risk? Reported underlying mechanisms include pelvic venous compression by the pregnant uterus, hormone- and uterus-related venous stasis, compression of the left iliac vein by the right iliac artery, and changes in procoagulant and anticoagulant pathways along with fibrinolytic mechanisms.[6–9] For example, plasma endogenous thrombin potential (a marker of prothrombotic potential) and plasminogen activator inhibitor-1 levels (markers of fibrinolytic activity) are significantly higher in pregnant people than in nonpregnant controls.[8,9] In pregnancy, platelets also undergo morphological changes and platelet activation is increased.[10] When they are activated, platelets release many signaling factors, known as the platelet releasate,[11] which plays crucial roles in wound healing, hemostasis, and inflammation.[12] Intriguingly, maternal platelet releasate contents differ in pregnant people compared with nonpregnant people. In a recent Irish study, 18 healthy pregnant and 13 nonpregnant platelet releasate were analyzed using comparative label-free quantitative proteomic profiling and the differences were characterized.[13] Sixty-nine PR proteins were differentially released, and it was possible to discriminate pregnant and nonpregnant people in the case of 11 PR proteins. It remains to be determined whether this change in platelet releasate contents contributes to pregnancy-associated VTE risk.

In this review, we provide an update on the recent evidence of known VTE risk factors in pregnancy, the frequency of these risk factors, and evidence-based prevention of VTE in people with prior VTE, anchoring to recently published randomized controlled trial (RCT) data. We outline knowledge gaps and current approaches to VTE prevention in the postpartum period, including ongoing pilot trials. Finally, we review recently published registry data on the incidence and prognosis of superficial vein thrombosis during pregnancy and the postpartum period.

VTE Risk Factors in Pregnancy

The higher pregnancy-associated VTE baseline risk can be increased by additional characteristics that can preexist or present during pregnancy or in the peripartum period.[6,14–21] This is why it is so crucial to carry out a VTE risk assessment at various time points in pregnancy, repeating this risk assessment postpartum or if risk factors change.[22] Risk factors can relate to personal characteristics (age, body mass index [BMI], smoking), previous medical history (history of VTE, inflammatory disease), or current pregnancy (preeclampsia, preterm delivery, mode of delivery). They can be classified according to their strength of association with VTE: very strong (e.g., personal history of VTE), strong (e.g., emergency cesarean delivery, morbid obesity), and weak (e.g., age ≥35 years). Literature pertaining to the strength of risk factors, in terms of their odds ratios (ORs) for VTE, has been summarized by the authors in detail in previous reviews.[6,23,24]

How Frequently and When Do Pregnancy-Associated VTE Risk Factors Occur?

The relationship between VTE risk variables and the risk of pregnancy-associated VTE varies; however, we now know that, certainly when assessed in the postpartum period, these risk factors are multiple and common (►Table 1).[25] According to a recently published cross-sectional study of prospectively collected data from 21,019 sequential postpartum VTE risk assessments completed over a 3-year period in the Rotunda Hospital, Dublin, Ireland, the most frequent VTE risk factors related to maternal characteristics and delivery characteristics included overweight status and obesity (36%), age ≥ 35 years (35%), and cesarean delivery (32%).[25] In total, 78% of people had at least one VTE risk factor, and 40% of them had several risk factors (two or more). The crucial necessity of doing a VTE risk assessment after delivery is shown by the fact that in 19% of people, all VTE risk factors occurred during delivery or in the postpartum period (and were not present prior to this peripartum time).[25]

Thrombophilia

People with hereditary and acquired thrombophilia are more likely to experience pregnancy-associated VTE than people without these disorders, especially if they also have a family history of VTE.[26–29] The reported increase in pregnancy-associated VTE risk varies significantly between studies and by thrombophilia type. The acceptable threshold for starting thromboprophylaxis during pregnancy, according to experts from the American Society of Hematology's (ASH) guidelines panel, is approximately 2%.[26] In some thrombophilias, the absolute risk of VTE during pregnancy does not appear to cross this threshold, while it does in others. For instance, in a pooled analysis of published cohort studies including thrombophilic women with a family history of VTE reported in the 2018 ASH guideline, an absolute risk of 0.5% (95% CI: 0.06–1.21%) was estimated.[26] This is not surprising, given the results of a more general case control study including 437 first-degree relatives of 112 symptomatic heterozygous factor V Leiden (FVL) mutation carriers (and 30 relatives of 6 homozygous FVL carriers) reported annual VTE incidences of 0.45% (95% CI: 0.28–0.61%) in FVL mutation–positive relatives of propositi who were heterozygous FVL carriers and 0.10% (CI: 0.02–0.19%) in those who did not have the mutation (relative risk [RR]: 4.2 [CI: 1.8–9.9]).[30] Notably, 30% of VTE events were associated with pregnancy or use of oral contraceptives.

Prior Venous Thromboembolism

VTE is much more likely to occur in pregnant people with a personal history of VTE[16,31] than in those without a history of VTE. The reported absolute risk in the absence of thromboprophylaxis is estimated at 2 to 6% in the antepartum[32–34] and 6 to 8% in the postpartum period,[31,33,34] and it appears to be highest for people with an unprovoked or a hormone-related VTE in these cases. In comparison to people who had an unprovoked or nonhormonal transient risk

Table 1 Prevalence of postpartum VTE risk factors among people delivering an infant >24 weeks' gestation and undergoing VTE risk assessment between January 2015 and December 2017 in a single center

VTE risk factor (RF)	No. of people ($N = 21,019$)	% with RF (95% CI)
Overweight or obesity	7,536	36 (35–37)
Overweight (BMI 25.1–29.9)	4,391	21 (20–21)
Obese class I and II (BMI 30–39.9)	2,837	14 (13–14)
Obese class III (BMI >40)	308	1.5 (1.3–1.6)
Age ≥35 y	7,302	35 (34–35)
Operative vaginal delivery	3,751	18 (17–18)
Emergency cesarean delivery	3,578	17 (17–18)
Planned cesarean delivery	3,139	15 (15–15)
Parity ≥3	1,482	7.1 (6.7–7.4)
Smoker	1,376	6.6 (6.2–6.9)
Preterm delivery (<37 wk of gestation)	1,366	6.5 (6.2–6.8)
PPH > 1,000 mL or blood transfusion	748	3.6 (3.3–3.8)
High-risk family history of VTE	406	1.9 (1.8–2.1)
Prolonged labor	401	1.9 (1.7–2.1)
Multiple pregnancy	346	1.7 (1.5–1.8)
IUGR	341	1.6 (1.5–1.8)
Severe medical comorbidity	328	1.6 (1.4–1.7)
Gross varicose veins	314	1.5 (1.3–1.7)
Preeclampsia	314	1.5 (1.3–1.7)
MROP	274	1.3 (1.2–1.5)
Immobility	205	1.0 (0.9–1.1)
Previous VTE	114	0.5 (0.5–0.7)
Stillbirth	100	0.5 (0.4–0.6)
Systemic infection	92	0.5 (0.4–0.5)
Thrombophilia	81	0.4 (0.3–0.5)

Abbreviations: BMI, body mass index; IUGR, intrauterine growth restriction; MROP, manual removal of the placenta; PPH, postpartum hemorrhage; VTE, venous thromboembolism.
Source: O'Shaughnessy et al.[25]

factor–provoked event, people with a history of a VTE event in the presence of oral hormonal contraceptive use or pregnancy experienced a higher VTE recurrence rate during pregnancy (although this finding did not reach statistical significance).[33,34] In addition, a sizable retrospective cohort study found that people with pregnancy-associated VTE had a greater risk of recurrence during a future pregnancy than people with unprovoked VTE (4.5 vs. 2.7%; RR: 1.7; 95% CI: 1.0–2.8).[35] However, among people whose past incident was triggered by a significant transitory nonhormonal VTE risk factor, the chance of VTE recurrence during pregnancy was predicted to be 1.0% (95% CI: 1.9–5.7%).[7]

Interaction of VTE Risk Factors during Pregnancy and in the Postpartum Period

Although the frequency and risk of individual VTE risk factors has been characterized in multiple observational studies, an important knowledge gap still exists surrounding the duration of the increased risk and the interaction of VTE risk factors with each other, which requires a high statistical power and thus very large sample sizes.

The possibility that individual risk factors impact the risk of postpartum VTE for different durations would have clinical implications, but this has not been investigated thoroughly. One large United Kingdom retrospective cohort has suggested that people who are obese, with preeclampsia, infection, or those with cesarean delivery have persistently elevated risks for 6 weeks, while the risk of those with postpartum hemorrhage (PPH) or preterm birth was only elevated for 3 weeks after delivery.[36] This adds uncertainty to the optimal duration of postpartum thromboprophylaxis, which is largely unknown.

With regard to the combination of risk factors, a Norwegian hospital-based case control study offered an intriguing perspective. In total, 559 people with objectively confirmed VTE during pregnancy or the postpartum period and 1,229 controls were enrolled in this study.[15] Some risk factors

exhibited additive interaction (as seen with the combination of assisted reproductive technology [ART] with multiple pregnancy and emergency cesarean section [CS] with infection), while others appeared to act as multipliers. For example, adjusted ORs of antepartum immobilization in people with BMI of <25 and ≥ 25 kg/m^2 were 7.7 (95% CI: 3.2–19.0) and 62.3 (95% CI: 11.5–337.6), respectively. We view these findings as exploratory, given the wide confidence intervals around these possible interactions and the possibility of selection bias in this study.

Understanding how these VTE risk variables affect absolute pregnancy-associated VTE in particular is crucial. A risk prediction model for postpartum VTE was derived and externally validated, utilizing data from 433,353 deliveries in the United Kingdom Clinical Practice Research Datalink linked to Hospital Episode Statistics. In total, 662,387 deliveries in Swedish datasets were used to externally validate this model. The strongest VTE predictors in the final multivariable model were emergency CS, stillbirth, varicose veins, preeclampsia/eclampsia, infection, and medical comorbidities. The model performed reasonably well in predicting postpartum VTE with a C statistic of 0.70 (95% CI: 0.67–0.73) in the United Kingdom cohort and 0.73 (95% CI: 0.71–0.75) in the Swedish cohort.[20] Limitations of this tool lie in possible bias from misclassification of VTE events and of risk factors in both development and validation efforts, the fact that it should not be used for people with thrombophilia, and that very few people have predicted postpartum VTE risks greater than 0.2 to 1%.

Reducing the Risk of VTE in Pregnancy

Two VTE prevention strategies are expected to be most effective: the prevention of postpartum VTE among people with risk factors, as the incidence of pregnancy-associated VTE peaks in the 3 weeks after delivery, and the prevention of pregnancy-associated VTE among people with a prior VTE, who have the greatest risk.

However, answering the question "Does pharmacological thromboprophylaxis reduce the risk of pregnancy-associated VTE?" has proven to be difficult. In fact, a 2014 Cochrane review's authors came to the conclusion that "there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy (and that) large scale, high-quality randomised [sic] trials of currently used interventions are warranted."[37] The same conclusions arise from a recent (2023) systematic review and meta-analysis, stating that the existing literature is insufficient.[38]

VTE Risk Reduction in People with Prior VTE

The multicenter, multinational academic *Highlow* RCT was published in 2022 and tested the risk–benefit of two doses of low-molecular-weight heparin (LMWH) during pregnancy and the postpartum period in women at high risk of VTE.[39] This RCT included 1,110 pregnant people aged ≥ 18 years and ≤ 14 weeks' gestation with a history of prior objectively confirmed VTE (either unprovoked/provoked by a hormonal-/pregnancy-related risk factor). Nine countries took part in the study with 70 sites in total. People were randomized to weight-adjusted intermediate-dose or fixed low-dose LMWH. No significant difference was observed in the primary efficacy outcome of objectively confirmed, adjudicated VTE up to 6 weeks postpartum. The primary outcome was reported in 3 and 2% of people in the low- and intermediate-dose groups, respectively (RR: 0.69 [95% CI: 0.32–1.47]; $p = 0.33$). There was also no significant difference between the groups in the primary safety outcome, major bleeding (RR: 1.16 [95% CI: 0.65–2.09]). Based on this study, low-dose LMWH is appropriate for prevention of recurrent VTE in pregnancy, although the risk of VTE despite prophylaxis is not negligible. Interestingly, antepartum VTE was numerically similar in both study arms (1% in both), whereas postpartum VTE recurrence was more frequent in those receiving low-dose LMWH compared with intermediate-dose LMWH (2 and 1%, respectively). While this suggests the hypothesis that intermediate-dose LMWH may be more favorable after delivery or in the late third trimester, this finding is exploratory and needs confirmation in future randomized controlled studies.

Pregnancy-Associated VTE Risk Reduction in People with Multiple, Common VTE Risk Factors

Following the publication of data from the *Highlow* study,[39] we now have high-quality data to support optimal management of pregnant people who have a personal prior VTE history. However, this risk factor is thankfully uncommon among the entire pregnant population (0.5% [95% CI: 0.5–0.7%] of all people recruited to a recent large observational study[25]). Wide variations in worldwide guideline recommendations,[22,26,40–42] as well as heated debate,[43,44] demonstrate the important information gap that still exists about the best method for pregnancy-associated VTE prevention in people with more prevalent VTE risk factors. It is noteworthy that the 2018 ASH guideline panel[26] emphasized critical research requirements, including a desire for greater evidence on the absolute VTE risk in people with combinations of known risk factors, and that the balance of thrombosis and bleeding risk remains uncertain.

A multicenter study conducted by the STRATHEGE investigators of the French INNOVTE Network evaluated the rates of pregnancy-associated VTE and placental vascular complications before and after a risk scoring system was put in place to identify antenatal and postpartum thromboprophylaxis techniques in 2,085 people with major VTE risk factors. Before and after the application of risk score–driven prophylaxis, vascular incidents (pregnancy-associated VTE including SVT and placental vascular complications) occurred in 190 (19.2%) and 140 (13%) cases, respectively (RR: 0.68 [95% CI: 0.55; 0.83]), with an associated increase of low-dose LMWH use during pregnancy and puerperium from 59 to 71%. In addition, there was a decrease in the incidence of pregnancy-associated DVT (RR: 0.30 [95% CI: 0.14; 0.67]), mainly driven by a reduction of antepartum SVT. PPH was noted in 3.2% of people prior to implementation and 4.5% afterward (RR: 1.38 [95% CI: 0.89; 2.13]; $p = 0.15$).[45] These findings are encouraging, with improved outcomes following a risk score and a greater use of LMWH, but given the lack of randomization these cannot be interpreted as causal and definite.

Postpartum Prevention

Conducting RCTs for people with (in this case, postpartum) VTE risk factors can prove to be quite difficult, as the PROSPER investigators' experience has shown.[46,47] To ascertain the viability of carrying out a full-scale multicenter trial, Rodger et al conducted a multinational, double-blind pilot RCT comparing LMWH for 21 days with placebo injections in postpartum people at high VTE risk.[46] In six centers, recruiting for a mean of 6.3 months, with a recruitment rate of 0.7 per site per month and just 25 (6.6%) of the 378 eligible people being randomized, the authors came to the conclusion that a double-blind RCT design for this intervention was not practical in North America. The feasibility of a randomized, open-label trial contrasting 10 days of LMWH medication with no treatment for postpartum thromboprophylaxis in people at risk of VTE was investigated in a second pilot study by the same team.[47] With a recruitment rate of 0.9 per center each month, only 37 of the 343 eligible people were randomized throughout 4.9 months. According to the authors, "poor recruitment is a frequent and significant threat to the completion of RCTs, especially notable in the peri-partum population." As a result, guideline recommendations are currently primarily based on expert opinion rather than high-quality data.[22,26,41,48,49] The conflicting dangers and difficulties of pharmaceutical thromboprophylaxis, which are rather prevalent[50] and include bleeding, bruising, skin responses, pain, possible increased wound complications,[51] and, in many jurisdictions, significant out-of-pocket costs, can make this highly challenging for health care professionals.

Surprisingly, the difficulty of conducting trials of postpartum thromboprophylaxis contrasts with the views and preferences of people. Very recently, in the "PREFER-Postpartum" study, we elicited the desire for postpartum thromboprophylaxis among 122 pregnant/postpartum people in Geneva and Paris. Using structured interviews, most people favored receiving short-term postpartum prophylaxis with LMWH, even at low projected risks of postpartum VTE (0.1%). This result was somewhat sensitive to the bleeding risk associated with the drugs and varied substantially across people. Hence, while postpartum people are reluctant to participate in clinical trials, most value measures to prevent postpartum VTE.[52]

The lack of strong evidence for the risk–benefit of LMWH has led to extremely varying guidance and clinical practice. We recently conducted an analysis of prospectively collected Irish data from 21,019 continuous comprehensive postpartum VTE risk assessments, applying the recommendations of representative international guidelines, and calculating the percentage of people who would have received a recommendation for postpartum thromboprophylaxis under each guideline.[25] This analysis was done to reflect the lack of data. According to the recommendations from the American College of Obstetricians and Gynecologists (ACOG)[53] and the Royal College of Obstetricians and Gynaecologists (RCOG)[22] of the United Kingdom (►Table 2), the percentage of people

Table 2 Estimated proportion of people recommended postpartum thromboprophylaxis according to international guidelines

Guideline	Year	Jurisdiction	Estimated proportion of people recommended postpartum thromboprophylaxis ($N = 20,775$)					
			Total ($N = 21,019$)		Caesarean delivery ($n = 6,717$)		Vaginal delivery ($n = 14,302$)	
			n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Australia and New Zealand[42]	2012	Australia and New Zealand	4,895	23 (23–24)	4,559	68 (67–69)	336	2.3 (2.1–2.6)
American College of Chest Physicians (ACCP)[41]	2012	United States	1,521	7 (6.9–7.6)	1,435	21 (20–22)	86	0.6 (0.5–0.7)
American College of Obstetricians and Gynecologists (ACOG)[53]	2018	United States	1,678	8 (7.6–8.4)	1,594	24 (23–25)	84	0.6 (0.5–0.7)
National Partnership for Maternal Safety (NPMS)[59]	2016	United States	4,381	21 (20–21)	4,268	63 (62–65)	113	0.8 (0.7–1.0)
Royal College of Obstetricians and Gynaecologists (RCOG)[22]	2015	United Kingdom	7,858	37 (37–38)	5,673	85 (84–85)	2,185	15[15,16]
Swedish Society of Obstetrics and Gynecology (SFOG)[49]	2011	Sweden	2,302	11 (11–11)	2,074	31 (30–32)	228	1.6 (1.4–1.8)
Society of Obstetricians and Gynecologists of Canada (SOGC)[48]	2014	Canada	3,091	15 (14–15)	2,306	34 (33–36)	785	5.5 (5.1–5.9)

Abbreviation: CI, confidence interval.
Source: O'Shaughnessy et al.[25]

who would have received a recommendation for postpartum thromboprophylaxis ranged from 7 to 37%. A similar range from 9 to 40% was found in a similar work from Switzerland.[54]

We foresee different strategies to improve the evidence on postpartum thromboprophylaxis. The first is to test an oral drug to prevent postpartum VTE to eliminate the burden of subcutaneous injections. Unfortunately, the excretion of oral direct anticoagulants in maternal milk greatly limits their use.[55] Low-dose aspirin has some effect on VTE prevention, albeit weak.[56,57] This is the focus of the Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity (PARTUM) pilot trial, assessing the feasibility of randomizing people with some risk factors for postpartum VTE to 6 weeks of aspirin or placebo (NCT04153760). A second strategy is to infer the risk–benefit of LMWH from observational studies, but this is very challenging. Large sample sizes with varying prevalences of LMWH are required for the somewhat rare VTE outcome, with a need to limit VTE misclassification and to adjust for many confounding variables, with the persisting possibility of residual confounding. Retrospective before/after evaluations of protocols for postpartum VTE prevention in individual large hospitals have remained underpowered to detect differences in clinical outcomes.[58] A third strategy is to challenge the perception that a large-scale postpartum VTE is unfeasible. The Postpartum Heparin Against Venous Thromboembolism (PP-HEP) pilot trial in Geneva has recently shown that one out of four people was willing to participate in a pragmatic, open-label trial of 10 days of LMWH after delivery, with a promising recruitment rate, contrasting with previously pessimistic results in North America.[52]

We hope that this effort will be followed by a practice-changing randomized clinical trial to finally guide practice for postpartum thromboprophylaxis. While awaiting future data, how should we handle postpartum VTE prevention? There is agreement that people without any risk factors should not receive postpartum LMWH and that people at high risk (prior VTE, see below, or strong thrombophilia) should be administered LMWH. The clinical equipoise concerns people with some risk factors for VTE, usually in combination, where the evidence is insufficient. Here, hospital-based recommendations based on local preferences and individual shared decision-making are the only advisable processes at this time.

Conclusions

VTE is the leading cause of maternal mortality in developed countries. The pathophysiology of derangements in hemostasis during pregnancy are well described, at both the patient and molecular levels. Despite this, there remains a paucity of high-quality data surrounding optimal VTE prevention strategies for pregnant people. This lack of data is multifactorial, but it can largely be attributed to poor recruitment rates—particularly in the crucial postpartum period—as well as the fact that pregnant people are frequently excluded from clinical research studies. Encouragingly, recent efforts demonstrate that while postpartum people are reluctant to participate in clinical trials, they strongly value the prevention of postpartum VTE, and that the feasibility of a postpartum thromboprophylaxis trial is better than previously believed.[48]

At present, two prevention strategies prevail: preventing postpartum VTE among people with risk factors and preventing pregnancy-associated VTE among people with a prior VTE. Risk assessment is a fundamental component in combating pregnancy-associated VTE, and it is crucial to carry out a risk assessment at various points throughout pregnancy. It is important to classify risk factors by their strength of association with VTE. Even in thrombophilia, the indication for pharmacological VTE prophylaxis depends on the subtype. It is intriguing to consider the conjecture that risk factors in combination can exhibit additive or exponential interactions.[16] Similarly, the possibility that individual risk factors may impact the risk of postpartum VTE for different durations adds uncertainty to the optimum duration of postpartum thromboprophylaxis. Although highly susceptible to bias, a recently developed risk prediction model was shown to successfully distinguish between postpartum people with and without VTE. This is an exciting potential avenue in the pursuit of pregnancy-associated VTE prevention.

At present, strategies for prevention of pregnancy-associated VTE are based on expert opinion or observational data. Astonishingly, there is still insufficient evidence to confirm that pharmacological thromboprophylaxis reduces the risk of pregnancy-associated VTE.[35] Thankfully recent trials have aimed to bridge this knowledge gap and following the publication of data from the *Highlow* study,[39] we now have high-quality data to support optimal management of pregnant people who have a history of VTE. However, a question remains regarding the optimal dose in the postpartum period.

While the *Highlow* study succeeded in answering a critical clinical question, the evidence is still lacking for the vast majority of pregnant people who do not have the risk factor of prior VTE. Despite the fundamental challenges in conducting RCTs with pregnant people, we are optimistic that the recent phenomenal efforts will translate into clinical guidance. In the interim, individual risk assessments and shared decision-making remain the best practice.

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- Past Member of World Thrombosis Day International Steering Committee (http://www.worldthrombosisday.org/) (until 2021)
- Director at Large and Member, INVENT Council (International Network of VENous Thromboembolism Clinical Research Networks) https://www.invent-vte.com/
- Co-director, SPHERE Research Group, UCD Conway Institute
- Director, INViTE (Irish Network for VTE Research)
- Co-Founder (2016) and Member, Executive Committee of VTE Ireland, a National Clinical VTE Working Group
- Appointed to Advisory Committee for Human Medicine (ACHM) of the Health Products Regulatory Authority (HPRA) January 2016, Reappointed 2021
- Member of "Preventing venous thromboembolism in hospitals" Collaborative Advisory Group. Established May 2016; Chaired by Dr Philip Crowley, National Director, Health Services Executive Quality Improvement Directorate
- Board member, Thrombosis Ireland Patient Organization and Charity (Oct 2019-present)
- Oct 2019-present: Irish Haematology Society Transfusion Special interest Subcommittee
- Oct 2019-present: Irish Haematology Society Coagulation Special interest Subcommittee

References

1 Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol 2010;116(06):1302–1309
2 Knight M. Saving Lives, Improving Mothers' Care: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014–16. Oxford, UK: National Perinatal Epidemiology Unit; 2018
3 Konstantinides SV, Meyer G, Becattini C, et al. ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019;41(04):543–603
4 Abdul Sultan A, Tata LJ, Grainge MJ, West J. The incidence of first venous thromboembolism in and around pregnancy using linked primary and secondary care data: a population based cohort study from England and comparative meta-analysis. PLoS One 2013;8(07):e70310
5 Wiegers HMG, Körmendiné Farkas D, Horváth-Puhó E, Middeldorp S, van Es N, Sørensen HT. Incidence and prognosis of superficial vein thrombosis during pregnancy and the postpartum period: a Danish nationwide cohort study. Lancet Haematol 2023;10(05):e359–e366
6 Kevane B, Donnelly J, D'Alton M, Cooley S, Preston RJ, Ní Ainle F. Risk factors for pregnancy-associated venous thromboembolism: a review. J Perinat Med 2014;42(04):417–425
7 Rodger M. Pregnancy and venous thromboembolism: 'TIPPS' for risk stratification. Hematology (Am Soc Hematol Educ Program) 2014;2014(01):387–392
8 Egan K, O'Connor H, Kevane B, et al. Elevated plasma TFPI activity causes attenuated TF-dependent thrombin generation in early onset preeclampsia. Thromb Haemost 2017;117(08):1549–1557
9 Haire G, Egan K, Parmar K, et al. Alterations in fibrin formation and fibrinolysis in early onset-preeclampsia: association with disease severity. Eur J Obstet Gynecol Reprod Biol 2019;241:19–23
10 Morrison R, Crawford J, MacPherson M, Heptinstall S. Platelet behaviour in normal pregnancy, pregnancy complicated by essential hypertension and pregnancy-induced hypertension. Thromb Haemost 1985;54(03):607–611
11 Heijnen HF, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ. Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood 1999;94(11):3791–3799
12 Nurden AT. Platelets, inflammation and tissue regeneration. Thromb Haemost 2011;105(Suppl 1):S13–S33
13 Szklanna PB, Parsons ME, Wynne K, et al. The platelet releasate is altered in human pregnancy. Proteomics Clin Appl 2019;13(03):e1800162
14 Lindqvist P, Dahlbäck B, Marsâl K. Thrombotic risk during pregnancy: a population study. Obstet Gynecol 1999;94(04):595–599
15 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(06):905–912
16 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(05):1311–1315
17 Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. J Obstet Gynaecol Can 2009;31(07):611–620
18 Danilenko-Dixon DR, Heit JA, Silverstein MD, et al. 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(02):104–110
19 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(01):56–60
20 Sultan AA, West J, Grainge MJ, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ 2016;355:i6253
21 Sultan AA, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood 2013;121(19):3953–3961
22 Royal College of Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. RCOG Green-top Guideline No. 37a. London: Royal College of Obstetricians and Gynaecologists; 2015
23 Ewins K, Ní Ainle F. VTE risk assessment in pregnancy. Res Pract Thromb Haemost 2019;4(02):183–192
24 O'Shaughnessy F, O'Reilly D, Ní Áinle F. Current opinion and emerging trends on the treatment, diagnosis, and prevention of pregnancy-associated venous thromboembolic disease: a review. Transl Res 2020;225:20–32

25 O'Shaughnessy F, Donnelly JC, Bennett K, Damkier P, Áinle FN, Cleary BJ. Prevalence of postpartum venous thromboembolism risk factors in an Irish urban obstetric population. J Thromb Haemost 2019;17(11):1875–1885

26 Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv 2018;2(22):3317–3359

27 Robertson L, Wu O, Langhorne P, et al; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2006;132(02):171–196

28 Martinelli I, Legnani C, Bucciarelli P, Grandone E, De Stefano V, Mannucci PM. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001;86(03):800–803

29 Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. Blood 2016;128(19): 2343–2349

30 Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med 1998;128(01):15–20

31 Bleker SM, Buchmüller A, Chauleur C, et al. Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomised trial of two doses. Thromb Res 2016;144:62–68

32 Brill-Edwards P, Ginsberg JS, Gent M, et al; Recurrence of Clot in This Pregnancy Study Group. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. N Engl J Med 2000;343(20):1439–1444

33 De Stefano V, Martinelli I, Rossi E, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol 2006;135(03):386–391

34 Pabinger I, Grafenhofer H, Kaider A, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost 2005;3(05):949–954

35 White RH, Chan WS, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb Haemost 2008;100(02):246–252

36 Abdul Sultan A, Grainge MJ, West J, Fleming KM, Nelson-Piercy C, Tata LJ. Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort study from England. Blood 2014;124(18):2872–2880

37 Bain E, Wilson A, Tooher R, Gates S, Davis LJ, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev 2014; (02):CD001689

38 Oakes MC, Reese M, Colditz GA, et al. Efficacy of postpartum pharmacologic thromboprophylaxis: a systematic review and meta-analysis. Obstet Gynecol 2023;141(04):697–710

39 Bistervels IM, Buchmüller A, Wiegers HMG, et al; Highlow Block writing committee Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet 2022;400(10365):1777–1787

40 James A. Practice bulletin no. 123: thromboembolism in pregnancy. Obstet Gynecol 2011;118(03):718–729

41 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–e736S

42 McLintock C, Brighton T, Chunilal S, et al; Councils of the Society of Obstetric Medicine of Australia and New Zealand Australasian Society of Thrombosis and Haemostasis. Recommendations for the prevention of pregnancy-associated venous thromboembolism. Aust N Z J Obstet Gynaecol 2012;52(01):3–13

43 Kotaska A. Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens. BJOG 2018;125 (09):1109–1116

44 Arya R. Postpartum venous thromboembolism prophylaxis: harm versus benefit. BJOG 2018;125(09):1117

45 Chauleur C, Gris JC, Laporte S, et al; STRATHEGE Investigators and The STRATHEGE Group. Benefit of risk score-guided prophylaxis in pregnant women at risk of thrombotic events: a controlled before-and-after implementation study. Thromb Haemost 2018; 118(09):1564–1571

46 Rodger MA, Phillips P, Kahn SR, James AH, Konkle BAPROSPER Investigators. Low-molecular-weight heparin to prevent postpartum venous thromboembolism. A pilot randomised placebo-controlled trial. Thromb Haemost 2015;113(01):212–216

47 Rodger MA, Phillips P, Kahn SR, et al; PROSPER Investigators: Tim Ramsay, Dean Fergusson, Anne McLeod, Wee Shian Chan, Rshmi Khurana, Kara Narenberg, Haim Abenhaim, John Heit, Ghada Bourjeilly, Paul Gibson, Kent Bailey. Low molecular weight heparin to prevent postpartum venous thromboembolism: a pilot study to assess the feasibility of a randomized, open-label trial. Thromb Res 2016;142:17–20

48 Chan WS, Rey E, Kent NE, et al; VTE in Pregnancy Guideline Working Group Society of Obstetricians and Gynecologists of Canada. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can 2014;36(06):527–553

49 Lindqvist PG, Hellgren M. Obstetric thromboprophylaxis: the Swedish guidelines. Adv Hematol 2011;2011:157483

50 Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005;106(02):401–407

51 Ferres MA, Olivarez SA, Trinh V, Davidson C, Sangi-Haghpeykar H, Aagaard-Tillery KM. Rate of wound complications with enoxaparin use among women at high risk for postpartum thrombosis. Obstet Gynecol 2011;117(01):119–124

52 Blondon M, Lansiaux M, Bryan S, et al. Preferences of pregnant women for postpartum thromboprophylaxis: the bicentric PREFER-PP study. Res Pract Thromb Haemost 2023;7 (Suppl):1117

53 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 196: thromboembolism in pregnancy. Obstet Gynecol 2018;132(01): e1–e17

54 Gassmann N, Viviano M, Righini M, Fontana P, Martinez de Tejada B, Blondon M. Estimating the risk thresholds used by guidelines to recommend postpartum thromboprophylaxis. J Thromb Haemost 2021;19(02):452–459

55 Daei M, Khalili H, Heidari Z. Direct oral anticoagulant safety during breastfeeding: a narrative review. Eur J Clin Pharmacol 2021;77(10):1465–1471

56 Simes J, Becattini C, Agnelli G, et al; INSPIRE Study Investigators (International Collaboration of Aspirin Trials for Recurrent Venous Thromboembolism) Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. Circulation 2014;130(13):1062–1071

57 Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. Lancet 2000;355(9212):1295–1302

58 Robison E, Heyborne K, Allshouse AA, Valdez C, Metz TD. Implementation of a risk-based heparin protocol for postpartum venous thromboembolism prevention. Obstet Gynecol 2017;130 (02):262–269

59 D'Alton ME, Friedman AM, Smiley RM, et al. National partnership for maternal safety: consensus bundle on venous thromboembolism. Obstet Gynecol 2016;128(04):688–698

