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STATE OF THE ART ISTH 2019

VTE risk assessment in pregnancy

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Abstract

A State of the Art lecture, "VTE Risk Assessment in Pregnancy," was presented at the ISTH congress in Melbourne, Australia, in 2019. Venous thromboembolism (VTE) remains a leading cause of death in pregnancy and in the postpartum period. Moreover, VTE can result in lifelong disability. The elevated baseline pregnancy-associated VTE risk is further increased by additional maternal, pregnancy, and delivery characteristics, highlighting the importance of VTE risk assessment in early pregnancy, at delivery, and if risk factors change. This review will provide an overview of the impact and epidemiology of VTE in pregnancy (including reported risk factors for pregnancy-associated VTE), will address VTE risk-reduction strategies (including ongoing studies), and will provide a summary of critical knowledge gaps. Finally, throughout this review, relevant new data presented during the 2019 ISTH annual congress in Melbourne will be summarized.

KEYWORDS

postpartum, pregnancy, prevention, risk factors, venous thromboembolism

Essentials

- The following knowledge gaps need to be addressed by current and future research to better prevent pregnancy-associated VTE events:
- Pregnancy-associated venous thromboembolism (VTE) is a leading cause of maternal mortality and morbidity.
- Knowledge and awareness of VTE risk factors is vital to ensure that appropriate risk-reduction measures are implemented.
- VTE risk assessment should be performed in early pregnancy, at delivery, and if risk factors change.
- Several important knowledge gaps remain and should be prioritized for research to protect the health and lives of pregnant and postpartum women.

1 | INTRODUCTION

Venous thromboembolism (VTE) remains a leading cause of death in pregnancy and in the postpartum period.[1]. During 2014-2016, VTE was reported to be the top cause of direct maternal death in the United Kingdom and Ireland, occurring in 1.39 (95% confidence interval [CI], 0.95-1.96) per 100 000 pregnancies.[2] A maternal death due to pulmonary embolism is a devastating event with wide-reaching consequences for the woman's family, friends, and society. Importantly, VTE can also result in lifelong disability.[3] VTE risk rises during pregnancy and peaks in the postpartum period. In a recent systematic review and meta-analysis restricted to recent studies in which VTE cases were validated, the pooled incidence rate of VTE during the antepartum period was 118 (95% CI, 101-137) per 100 000 person-years and 424 (95% CI, 238-755) per 100 000 person-years during the postpartum period.[4] Mechanisms underlying this pregnancy-related increase in VTE risk

include venous stasis, pelvic venous compression by the gravid uterus, pulsatile compression of the left iliac vein by the right iliac artery and changes in pro- and anticoagulant and fibrinolytic pathways.[5–8] For example, plasma endogenous thrombin potential and plasminogen activator inhibitor-1 levels are significantly higher in pregnant women compared with nonpregnant controls.[7,8]

In pregnancy, platelets undergo morphological changes and their activation is increased.[9] Upon activation, platelets release a multitude of signaling (soluble and vesicular) factors collectively termed the *platelet releasate* (PR),[10] which plays important roles in hemostasis, wound healing, and inflammatory response.[11] Maternal PR enhances trophoblast invasion and drives placental bed angiogenesis, critical processes during normal placentation.[12] Recently, PR contents of 18 healthy pregnant and 13 nonpregnant women were characterized using comparative label-free quantitative proteomic profiling and shown to be altered in pregnant compared with nonpregnant women.[13] Sixty-nine PR proteins were differentially released, and 11 PR proteins were capable of discriminating pregnant and nonpregnant women with an area under the curve of 0.876, sensitivity of 88.9%, and specificity of 84.6%. It remains to be determined whether this change in PR contents contributes to pregnancy-associated VTE (PA-VTE) risk.

1.1 | ISTH 2019 (Melbourne) report

De Laurenzo and colleagues[14] evaluated thromboelastography parameters in 70 healthy pregnant or postpartum women, reporting a lower "K" parameter and higher "alpha angle" and "maximum amplitude (MA)" parameters in the first trimester compared with the postpartum period, overall suggesting a prothrombotic state using this assay in the postpartum period. Another multicenter cross- sectional cohort study by Obeng-Tuudah and colleagues including 175 women showed that platelet function (measured by light transmission aggregometry in response to 6 agonists) demonstrated a non–statistically significant increase with advancing pregnancy, reaching highest levels in the third trimester and reverting to control levels postpartum.[15]

2 | ADDITIONAL PA-VTE RISK FACTORS

This elevated baseline PA-VTE risk is further increased by additional maternal, pregnancy, and delivery characteristics (Table 1),[5,16–23] highlighting the importance of VTE risk assessment in early pregnancy, at delivery, and throughout pregnancy if risk factors change (eg, during extended antenatal immobilization, as will be discussed later).[24]

2.1 | Thrombophilia

PA-VTE risk is higher in women with inherited and acquired thrombophilia compared with those without these conditions, particularly if associated with a family history of VTE.[25–28] The reported increase in PA-VTE risk varies widely depending on the type of thrombophilia and between studies. The American Society of Hematology (ASH) guideline panel has suggested that the appropriate threshold for initiation of thromboprophylaxis during pregnancy is approximately 2%.[25] Absolute risks of VTE during pregnancy appear not to reach this threshold in the case of some thrombophilias but do with others. For example, in a recent case-control study, the absolute reported

TABLE 1 aOR and IRR reported for selected maternal, pregnancy, and delivery characteristics in the listed studies

Maternal characteristics	
Risk factor	**Selected aOR/IRR (95% CI)**
Age > 35 y	1.3 (1.0-1.7)[16]
Parity ≥ 3	2.4 (1.8-3.1)[16]
BMI ≥ 25kg/m^2	1.8 (1.3-2.4)[a,17]
BMI ≥ 25kg/m^2 + antepartum immobilization	62.3 (11.5-337.6)[a,17]
Smoker[b]	2.1 (1.3-3.4)[a,17]
ART (singleton)	4.3 (2.0-9.4)[a,17]
Varicose veins[d]	2.21 (1.55-4.76)[a,23]
Inherited thrombophilia	Variable (0.7-34.4)[26]
Prior VTE	24.8 (17.1-36.0)[18]
Antiphospholipid syndrome	15.8 (10.9-22.8)[18]
Sickle cell disease	6.7 (4.4-10.1)[18]
Preexisting diabetes[d]	3.54 (1.13-11.0)[23]
Pregnancy Characteristics	
Risk factor	**Selected aOR (95% CI)**
IUGR	3.8 (1.4-10.2)[c,17]
Preeclampsia	3.1 (1.8-5.3)[c,17]
Twins	2.6 (1.1-6.2)[a,17]
Delivery characteristics	
Risk factor	**Sample aOR/IRR (95% CI)**
Preterm delivery[d]	2.28 (1.66-3.14)[c,23]
Emergency CS	2.7 (1.8-4.1)[c,17]
Stillbirth[d]	4.07 (1.73-9.56)[c,23]
Infection (CS)	6.2 (2.4-16.2)[c,17]
PPH ≥ 1000 mL	4.1 (2.3-7.3)[c,17]
Infection (VD)	20.2 (6.4-63.5)[c,17]

Note: The reported strength of these characteristics is highly variable between studies: the intention of this table is to raise awareness of the need to consider individualized risk assessment at these times in the pregnancy journey rather than to comprehensively review all reported risk factors.

Abbreviations: aOR, adjusted odds ratio; ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; CS, cesarean section; FHx, family history of VTE; IRR, incidence rate ratio; IUGR, intrauterine growth restriction; PPH, postpartum haemorrhage; VD, vaginal delivery.

[a]As a predictor of antenatal VTE events.

[b]10-30 cigarettes per day.

[c]As a predictor of postnatal VTE events.

[d]Denotes IRR rather than aOR.

risk of PA-VTE in women heterozygous for the factor V Leiden (FVL) polymorphism was 0.5% (95% CI, 0.23%-0.72%) in women aged <35 years [28] and in a pooled analysis of published studies including thrombophilic women with a family VTE history reported in the 2018 ASH guideline, an absolute risk of 0.5% (95% CI, 0.06%-1.21%) was estimated.[25] In contrast, the combination of compound heterozygosity for FVL and the prothrombin gene promoter region polymorphism (G20210A) is reported to be associated with an absolute PA-VTE risk of 5.5% (95% CI, 0%-21.92%).[28]

2.1.1 | ISTH 2019 (Melbourne) report

VTE risk in women with antithrombin deficiency was highlighted by Abbattista and colleagues in a single-center retrospective Italian study including women with quantitative (type I) antithrombin deficiency who had at least 1 pregnancy. Eighty women without current VTE had 189 pregnancies; 43 of whom were managed with low-molecular-weight heparin (LMWH) thromboprophylaxis and 146 without. PA-VTE occurred in 7.0% and 11.6%, respectively (relative risk [RR], 0.6; 95% CI, 0.2-1.9).

2.2 | Prior VTE

Women with a personal VTE history have a higher risk of recurrent VTE during pregnancy.[18,29] The absolute reported recurrence risk varies widely[30–33] but appears highest for women with an unprovoked or a hormone-provoked VTE, in which the reported absolute risk in the absence of thromboprophylaxis exceeded ~2% to 6% in some studies.[29–32,34] Two retrospective studies reported a higher VTE recurrence rate (although not reaching statistical significance) during pregnancy in women with a history of a VTE event provoked by oral hormonal contraceptive use or pregnancy than in women with an unprovoked or nonhormonal transient risk factor–provoked event.[31,32] Moreover, a large retrospective cohort study reported a higher risk of recurrence during pregnancy in women with pregnancy-associated VTE than women with unprovoked VTE (4.5% vs. 2.7%; RR, 1.7; 95% CI, 1.0-2.8).[35] In contrast, VTE recurrence risk during pregnancy was estimated to be 1.0% (95% CI, 1.9%-5.7%) in women whose prior event was provoked by a major transient nonhormonal VTE risk factor.[6]

2.3 | Interaction of PA-VTE risk factors

The interaction of VTE risk factors remains an important knowledge gap. However, an interesting insight was provided by a large hospital-based case-control study in which VTE risk factors were validated by review of medical records. This study included 559 women with objectively verified VTE during pregnancy or the postpartum period and 1229 controls.[17] Some risk factors exhibited *additive* interaction (as observed with the combination of assisted reproductive technology with multiple pregnancy, and emergency cesarean section with infection), while others appeared to act as *multipliers*, as with the combination of antepartum immobilization and elevated body mass index (the adjusted OR of antepartum immobilization in women with a body mass index 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).

In particular, understanding how these VTE risk factors translate into absolute PA-VTE is essential. A risk prediction model for postpartum VTE was recently developed using UK Clinical Practice Research Datalink data linked to Hospital Episode Statistics and including 433 353 deliveries. This model was externally validated using Swedish data sets and including 662 387 deliveries. Emergency cesarean section, stillbirth, varicose veins, preeclampsia/eclampsia, infection, and medical comorbidities were the strongest VTE predictors in the final multivariable model. The risk prediction model was able to discriminate postpartum women with and without VTE with a C statistic of 0.70 (95% CI, 0.67-0.73) in the UK cohort and 0.73 (95% CI, 0.71-0.75) in the Swedish cohort, with excellent calibration of observed vs. predicted VTE risks.[22]

2.4 | How frequently do PA-VTE risk factors occur?

VTE risk factors vary in their association with PA-VTE risk but appear to be common. In 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 common VTE risk factors related to maternal characteristics and delivery characteristics included overweight and obesity (36%), age ≥ 35 (35%) and cesarean delivery (32%). Over three-quarters of women had at least 1 VTE risk factor (78%), and over 40% had multiple (2 or more) VTE risk factors. In 19% of women, all VTE risk developed during delivery or in the postpartum period (and were not present prior to the peripartum period; Figure 1),[36] highlighting the critical importance of performing VTE risk assessment after delivery.

3 | REDUCING THE RISK OF VTE IN PREGNANCY

Addressing the question "does pharmacological thromboprophylaxis reduce the risk of PA-VTE" has been challenging, despite some progress in specific areas, which will be discussed. Indeed, the authors of a 2014 Cochrane review concluded that "there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy *(and that)* large scale, high-quality randomised trials of currently used interventions are warranted."[37] However, the experience of the PROSPER investigators has demonstrated that conducting randomized controlled trials (RCTs) for women with (in this case, postpartum) VTE risk factors can prove extremely challenging[38,39]: Rodger et al[38] conducted a multinational, double-blind pilot RCT comparing LMWH for 21 days vs.

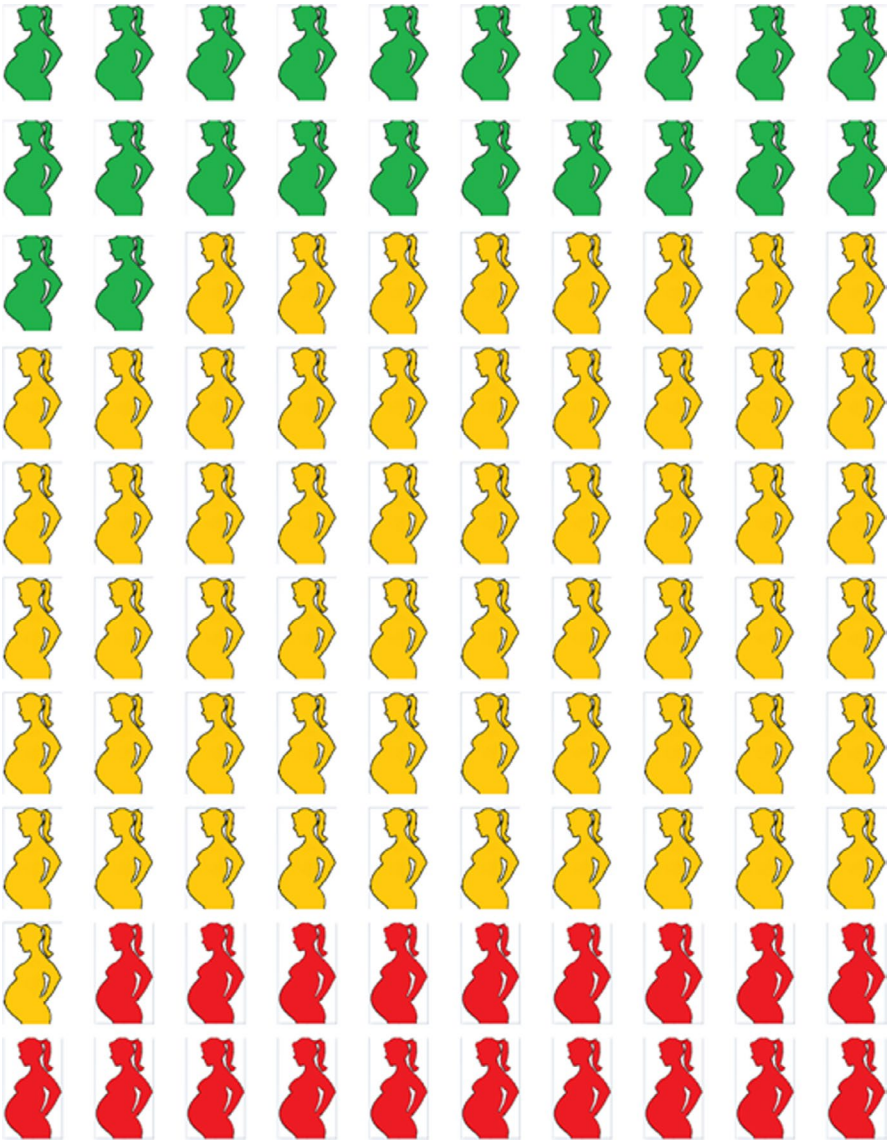

FIGURE 1 Frequency of VTE risk factors identified in postpartum women. Green: No VTE risk factors identified; Orange: at least one VTE risk factor identified; Red: VTE risk factors were not identifiable prior to labor and delivery or the postpartum period. FHx, family history; VTE, venous thromboembolism

placebo injections in postpartum women at high VTE risk to determine the feasibility of conducting a full-scale multicenter randomized double-blind study. Of 378 eligible women, only 25 (6.6%) were randomized, with a recruitment rate of 0.7 per center per month, leading the authors to conclude that a double-blind RCT design for this intervention was not feasible. A second pilot by the same group explored the feasibility of a randomized, open-label trial comparing 10 days of LMWH vs. no treatment for postpartum thromboprophylaxis in women at risk of VTE.[39] Of 343 eligible women, only 37 were randomized over 4.9 months, with an overall recruitment rate of 0.9 per center per month. The authors noted that "poor recruitment is a common and major threat to the completion of RCTs, especially notable in the peri-partum population."

Consequently, to date, guideline recommendations are mainly based on expert opinion rather than high-quality evidence.[24,25,40–42] This can be extremely difficult for care providers, particularly given the competing risks and challenges of pharmacological thromboprophylaxis, which are relatively common [43] and include bleeding, bruising, skin reactions, pain, and, in many jurisdictions, high out-of-pocket costs.

3.1 | What is the effect of LMWH on bleeding risk during pregnancy?

Despite the fact that the stakes are so high, there is a dearth of high-quality data surrounding the impact of LMWH on bleeding risk during pregnancy. A 2005 systematic review that aimed to assess the safety and efficacy of LMWH during pregnancy reported a 2.0% (95% CI, 1.50%-2.61%) overall risk of "significant maternal bleeding" for women receiving LMWH for thromboprophylaxis, adverse pregnancy outcome, or unspecified indications.[43] These events included antenatal bleeding (0.42%; 95% CI, 0.21%-0.75%), "primary obstetric causes" for bleeding (0.92%; 95% CI, 0.59%-1.37%), and wound hematoma (0.65%; 95% CI, 0.38%-1.04%). There is frequently no consistent definition of bleeding in studies

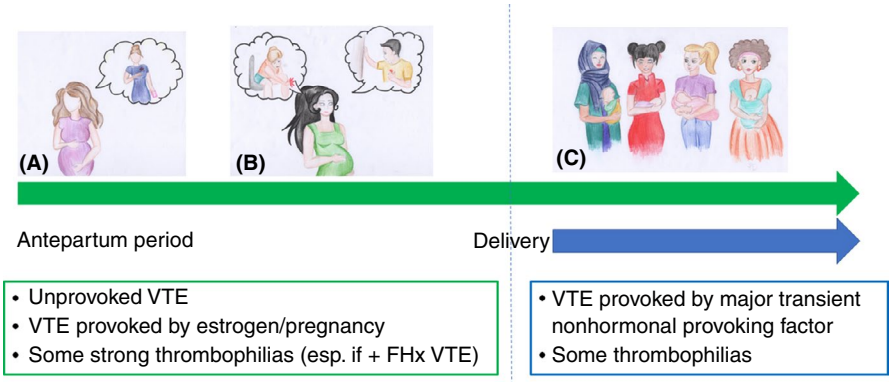

FIGURE 2 Prevention of VTE in women with prior VTE or thrombophilia. Guideline recommendations around VTE and thrombophilia can be broadly summarized as follows: Antepartum + postpartum thromboprophylaxis is recommended for women with prior unprovoked VTE or VTE provoked by estrogen or pregnancy (A) and for some strong thrombophilias, particularly if associated with a family history of VTE (B) due to a higher predicted recurrence risk than for women with a VTE provoked by major transient nonhormonal provoking factors and some weaker thrombophilias, for whom only postnatal thromboprophylaxis is recommended (C). FHx, family history; VTE, venous thromboembolism

evaluating LMWH in pregnancy. In a systematic review of RCTs in pregnant women evaluating the effect of LMWH, 16 studies met eligibility criteria, which included 2690 women. Critically, bleeding events were prospectively recorded using a standardized definition in only one-third (912 women).[44] The risk of major bleeding with LMWH appears low in both the heparin and no-heparin arms of RCTs.[6] Moreover, while minor bleeding is common in women in the heparin and no-heparin arms of RCTs comparing standard care or placebo to LMWH, it remains uncertain whether the risk is significantly higher with LMWH. Indeed, highly variable rates of minor bleeding have been reported in the heparin and no-heparin arms of RCTs.[44] Arising from this unmet clinical need, a new classification of anticoagulant-related bleeding has recently been proposed by the ISTH Scientific and Standardization Subcommittee on Control of Anticoagulation.[44]

3.2 | PA-VTE risk reduction in women with prior VTE

Women with a personal VTE history have a higher risk of recurrent VTE during pregnancy.[18,29] The absolute reported recurrence risk varies widely [30–33] but appears highest for women with an unprovoked or a hormone-provoked VTE, in which the reported absolute risk in the absence of thromboprophylaxis has exceeded ~2% to 6% in some studies.[29–32,34] It appears that this risk may be reduced with LMWH: Pooled proportions of recurrent major VTE reported in studies evaluating LMWH during the antepartum and postpartum periods in women with prior VTE (including provoked [nonestrogen], unprovoked, or estrogen-associated VTE as a single group) reported antepartum recurrence risks of 0.9% (95% CI, 0.5%-1.8%) with LMWH and 4.2% (95% CI, 0.3%-6.0%) without LMWH and postpartum recurrence risks of 1.7% (95% CI, 1.2%-2.7%) with LMWH and 6.5% (95% CI, 4.3%-9.7%) without LMWH.[6] Current American College of Chest Physicians (ACCP) and ASH guidelines recommend that all pregnant women with a history of VTE receive postpartum pharmacologic thromboprophylaxis with LMWH, while women with prior VTE that is either unprovoked or estrogen/pregnancy-associated receive both antepartum and postpartum thromboprophylaxis (Figure 2).[25,40] These recommendations reflect lower reported recurrence risks for women with provoked (nonhormonal) VTE than for women whose VTE was estrogen related or unprovoked: In a pooled analysis of 4 cohort studies, major antenatal VTE recurrence rates without prophylaxis were 1.1% (95% CI, 0.2%-5.8%) 6.4% (95% CI, 3.9%-10.4%) and 3.6% (95% CI, 1.4%-8.9%) for these 3 groups, respectively.[6]

Previous guidelines have suggested various approaches to VTE prevention in these women, with strategies including a low prophylactic or an intermediate (half-therapeutic) dose.[25,40] The optimal LMWH dose is unknown. The ongoing Highlow study (NCT 01828697; clinicaltrials.gov) is addressing this question in an investigator-initiated, multicenter, multinational RCT comparing a fixed low dose of LMWH with an intermediate weight-adjusted dose in the prevention of pregnancy-related VTE recurrence in women ≥18 years with a history of VTE and an indication for ante- and postpartum thromboprophylaxis who are recruited ≤14 weeks' gestation (Figure 3).[29]

3.2.1 | ISTH 2019 (Melbourne) report

Interim data from the Highlow RCT on obstetric outcome and anesthetic use in 541 women using antepartum LMWH were presented by Dr Bistervels on behalf of the Highlow investigators.[45] In this study, LMWH is discontinued at first signs of labor or 12 hours (for patients randomized to low-dose LMWH) or 24 hours (for patients randomized to intermediate-dose LMWH) prior to planned delivery. In this analysis, the median time interval between the last LMWH injection and delivery was 34 hours. Spontaneous onset of delivery occurred in 43.5% and 50% of women receiving low- and intermediate-dose LMWH (OR, 0.8; 95% CI, 0.6-1.1). Neuraxial anesthesia was administered to 53.7% of women with no difference between low and intermediate doses (53.3% vs. 54.2%; OR, 1.0; 95% CI, 0.7-1.4).

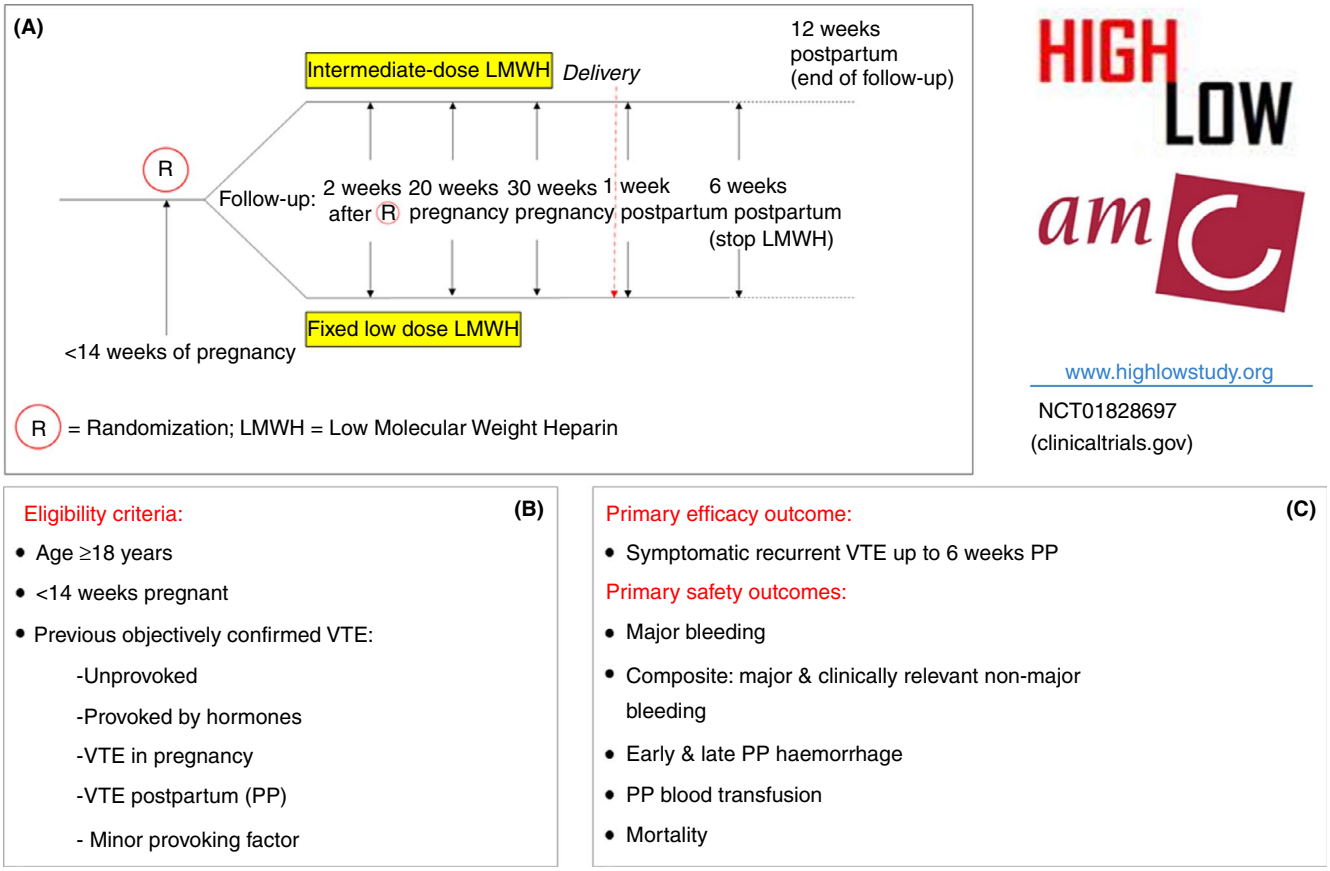

FIGURE 3 Overview of the Highlow study (www.highlowstudy.org; NCT01828697, clinicaltrials.gov). (A) Study flowchart from randomization to follow up; (B and C) Eligibility criteria, primary efficacy outcome, and primary safety outcomes

3.3 | PA-VTE risk reduction in women with thrombophilia

No randomized studies have explicitly evaluated the efficacy of pharmacological thromboprophylaxis in reducing PA-VTE risk in women with inherited thrombophilia. The TIPPS (Antepartum Dalteparin Versus No Antepartum Dalteparin for the Prevention of Pregnancy Complications in Pregnant Women With Thrombophilia) multinational RCT enrolled pregnant women with thrombophilia who were at increased risk of VTE or with previous placenta-mediated pregnancy complications and randomized participants to antepartum prophylactic LMWH dalteparin or to no antepartum dalteparin.[46] There was no significant difference in the primary composite outcome (severe or early-onset preeclampsia, small-for-gestational-age infant [birth weight < 10th percentile], pregnancy loss, or VTE). However, the study was not powered to specifically evaluate VTE risk reduction, and a relatively small number of participants were enrolled due to prior VTE (secondary VTE or calf deep vein thrombosis (DVT); 21 of 146 in the dalteparin arm and 15 of 143 in the no-dalteparin arm). Consequently, guideline recommendations for PA-VTE risk reduction in women with thrombophilia vary.[24,25,40,41,47] However, a consistent theme is the suggestion for implementation of ante- and postpartum thromboprophylaxis in pregnant women with "high-risk" thrombophilias, especially when accompanied by a strong family history (Figure 2), in which the predicted absolute VTE risk is above the ~2% threshold accepted in recent international guidelines but not for "low-risk" thrombophilias (eg, those associated with a <1% absolute predicted VTE risk).[25]

3.4 | PA-VTE risk reduction in women with multiple, common VTE risk factors

Although arguably the best-quality data exist to address PA-VTE risk reduction in women with a personal VTE history or inherited thrombophilia, these 2 categories of risk factor are rare (<1% in a recent large prospective study.[36]) The optimal strategy for PA-VTE prevention in women with more common VTE risk factors remains a critical knowledge gap, as evidenced (again) by widely varying international guideline recommendations[24,25,40,47,48] and intense debate.[49,50] In particular, the balance of thrombosis and bleeding risk is uncertain, and it is noteworthy that the 2018 ASH guideline panel highlighted important research needs, including a requirement for more data on the absolute VTE risk in women with combinations of known risk factors.[25] Reflecting the lack of data, we recently performed an analysis of prospectively collected data from 21 019 consecutive comprehensive postpartum VTE risk assessments, applying

the recommendations of representative international guidelines and calculating the proportion of women who would have received a recommendation for postpartum thromboprophylaxis under each guideline.[36] This proportion ranged from 7% under American College of Obstetrics and Gynecologists guidelines[51] to 37% under UK Royal College of Obstetricians and Gynaecologists guidelines[24] (Table 2).

Several international groups are prioritizing this research question (see, in particular, ISTH Melbourne report, below). In a recent retrospective cohort study by Cox and colleagues including 172 pregnancies in 123 women with a variety of VTE risk factors who qualified for enoxaparin thromboprophylaxis, the rate of VTE despite thromboprophylaxis was low at 1.2% (95% CI, 0.32-4.14).[33] A multicenter study performed by the STRATHEGE investigators of the French INNOVTE Network compared PA-VTE and placental vascular complication rates before and after implementation of a risk scoring system to determine thromboprophylaxis strategies in 2085 women. Vascular events occurred in 190 (19.2%) women before and 140 (13%) after implementation of risk score–driven prophylaxis (RR, 0.68; 95% CI, 0.55-0.83). Moreover, the incidence of PA-DVT was reduced (RR, 0.30; 95% CI, 0.14-0.67). Postpartum hemorrhage was recorded in 3.2% of women before and 4.5% after implementation (RR, 1.38; 95% CI, 0.89-2.13; $P = 0.15$).

3.4.1 | ISTH 2019 (Melbourne) report

Dr O'Shaughnessy of the Rotunda Hospital, Dublin, Ireland, presented pilot data evaluating the impact of systematic electronic VTE risk assessment [52] in all postpartum women combined with a strong positive campaign to increase VTE awareness among multidisciplinary colleagues on VTE prevention strategies in a large maternity hospital.[53] Introduction of these measures resulted in an increase in use of risk-appropriate pharmacological thromboprophylaxis (RA-TPX) from 68% to 89% ($P < 0.001$). This was primarily driven by increased use of RA-TPX after vaginal delivery (10%-72%) following the introduction of this tool ($P < .001$). Moreover, in this preliminary sample, hospital-level VTE events recorded at the institution during the delivery admission or in the postpartum period reduced from 22 (0.08%) in the 3-year period before introduction of "Thrombocalc" to 4 (0.02%) in the 3-year period after introduction of Thrombocalc (RR, 0.19; 95% CI, 0.07-0.56; $P < 0.001$), with the caveat that these VTE events were not adjudicated.

In an Australian single-center retrospective study including 153 women, Banahene and colleagues54 evaluated the efficacy and safety of standard-dose enoxaparin (40 mg) in prevention of pregnancy-associated VTE in obese women (defined in this study as body mass index ≥30 kg/m2 or weight >90 kg) compared to normal-weight women, approximately half of whom had a previous VTE history. A total of 77 pregnancies were included in the antepartum analysis, and 145 pregnancies in the postpartum analysis. [Corrections added on February 25, 2020, after first online publication: The values for above sentence updated.] No new antenatal VTE events occurred; however, 2 postpartum events were recorded, 1 in the obese group (1/53; 1.9%) and 1 in the nonobese group (1/93; 1.1%). Both patients had a history of prior VTE. Bleeding rates were similar in both groups.

Mezzarobba and colleagues[55] highlighted the potential overuse of LMWH during pregnancy in a 5-year retrospective analysis of women presenting to hematology and obstetrics outpatient clinics in Buenos Aires, Argentina. Only 37% of prescriptions were appropriate, according to ACCP 2012 recommendations.

TABLE 2 Estimated proportion of women recommended postpartum thromboprophylaxis according to international guidelines

			Estimated proportion of women recommended postpartum thromboprophylaxis (N = 20 775)					
			Total (N = 21 019)		Cesarean delivery (n = 6717)		Vaginal delivery (n = 14 302)	
Guideline	Year	Jurisdiction	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Australia and New Zealand [48]	2012	Australia and New Zealand	4895	23 (23-24)	4559	68 (67-69)	336	2.3 (2.1-2.6)
American College of Chest Physicians (ACCP) [40]	2012	United States	1521	7 (6.9-7.6)	1435	21 (20-22)	86	0.6 (0.5-0.7)
American College of Obstetricians and Gynecologists (ACOG) [51]	2018	United States	1678	8 (7.6-8.4)	1594	24 (23-25)	84	0.6 (0.5-0.7)
National Partnership for Maternal Safety (NPMS) [58]	2016	United States	4381	21 (20-21)	4268	63 (62-65)	113	0.8 (0.7-1.0)
Royal College of Obstetricians and Gynaecologists (RCOG) [24]	2015	United Kingdom	7858	37 (37-38)	5673	85 (84-85)	2185	15 (15-16)
Swedish Society of Obstetrics and Gynecology (SFOG) [42]	2011	Sweden	2302	11 (11-11)	2074	31 (30-32)	228	1.6 (1.4-1.8)
Society of Obstetricians and Gynecologists of Canada (SOGC) [59]	2014	Canada	3091	15 (14-15)	2306	34 (33-36)	785	5.5 (5.1-5.9)

Note: Reproduced, with permission, from O'Shaughnessy et al.[36]

The International Network of Venous Thromboembolism Clinical Research Networks (INVENT-VTE; https://www.invent-vte.com/) hosted an innovative "Dragon's Den" competition aimed at providing an international collaboration grant for an ambitious clinical trial addressing an important knowledge gap. This competition was won by Dr Leslie Skeith (University of Calgary and Canadian Venous Thromboembolism Clinical Trials and Outcomes Research) for the Pilot PARTUM Trial: Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity. PARTUM is a pilot study assessing the feasibility of an RCT evaluating aspirin in postpartum women at risk of developing VTE.

4 | VTE AWARENESS DURING PREGNANCY AND THE IMPORTANCE OF RISK ASSESSMENT

The international World Thrombosis Day campaign (https://www.worldthrombosisday.org/; @thrombosisday) aims to increase awareness of thrombosis and prevent death and disability due to this condition. This is highly relevant for pregnant women, their families, and their care providers. In a recent review of international guidelines on PA-VTE, 8 of 9 guidelines assessed recommended that all women should also undergo VTE risk factor assessment.[56] As discussed earlier, a substantial proportion of risk factors may arise for the first time in the peripartum or postpartum period, highlighting the importance of VTE awareness, not just in early pregnancy but also around the time of delivery. The reality of performing VTE risk assessment can be incredibly challenging, particularly in the often chaotically busy environment of the delivery suite or postnatal ward. However, we have recently demonstrated that, when this complex, multistep process is streamlined and tailored to this extremely busy environment with intense multidisciplinary stakeholder involvement, systematic risk assessment of a very high proportion of women is feasible.[52]

4.1 | ISTH 2019 (Melbourne) report

"Emphasis must be put on education and (VTE) awareness of pregnant women." This was the important message delivered by Ms Christine Ashimwe, World Thrombosis Day ambassador and founder, Rwanda Clot Awareness Network, who conducted a questionnaire-based cross-sectional study in 3 referral hospitals in Kigali city, which showed that knowledge of VTE was very low among pregnant women in Kigali, with only 9.33% and 15.7%, respectively, having "good knowledge" of VTE and treatment options respectively.[57]

5 | KNOWLEDGE GAPS

- Optimal LMWH dose for prevention of VTE recurrence in women with prior VTE
- Validation of clinical prediction tools evaluating absolute risk of VTE during antepartum and postpartum periods
- Optimal risk threshold for initiating pharmacological thromboprophylaxis in the antepartum and postpartum periods, particularly in women with lower-risk thrombophilic traits and multiple (common) VTE risk factors.
- Optimal duration of pharmacological thromboprophylaxis in the postpartum period
- Absolute bleeding risks and type of bleeding with pharmacologic thromboprophylaxis (eg, incisional versus uterine bleeding).

6 | CONCLUSIONS

Pregnancy-associated VTE can be a devastating event, with significant associated morbidity and mortality. Knowledge and awareness of VTE risk factors is vital to ensure that appropriate risk-reduction measures are implemented. Well-designed studies are ongoing and are likely to address important research questions in specific areas. However, important knowledge gaps remain, and these research areas should be prioritized to protect the health and lives of pregnant and postpartum women.

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AUTHOR CONTRIBUTION

Both KE and FNA wrote the manuscript.

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