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ORIGINAL ARTICLE

Estimating the value of future research into thromboprophylaxis for women during pregnancy and after delivery: a value of information analysis

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Abstract

Background: Risk assessment models (RAMs) are used to select women at increased risk of venous thromboembolism (VTE) during pregnancy and the puerperium for thromboprophylaxis.

Objectives: To estimate the value of potential future studies that would reduce the decision uncertainty associated with offering thromboprophylaxis according to available RAMs in the following groups: high-risk antepartum women (eg, prior VTE), unselected postpartum women, and postpartum women with risk factors (obesity or cesarean delivery).

Methods: A decision-analytic model was developed to simulate clinical outcomes, lifetime costs, and quality-adjusted life-years for different thromboprophylaxis strategies, including thromboprophylaxis for all, thromboprophylaxis for none, and RAM-based thromboprophylaxis. The expected value of perfect information analysis was used to determine which factors are associated with high decision uncertainty. The value of future research studies was estimated using expected value of sample information analysis. Costs were assessed from a health and social services perspective.

Results: The expected value of perfect information analysis identified high decision uncertainty for high-risk antepartum women (£21.8 million) and obese postpartum women (£13.4 million), which was largely attributable to uncertainty regarding the effectiveness of thromboprophylaxis in reducing VTE. A randomized controlled trial of thromboprophylaxis compared with none in obese postpartum women is likely to have substantial value (£2.8 million; 300 participants per arm). A trial in women with previous VTE would have higher value but would be less acceptable.

Conclusion: Future research should focus on estimating the effectiveness of thromboprophylaxis in obese postpartum women with additional risk factors who have not had a previous VTE.

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KEYWORDS
cost-benefit analysis, heparin, low-molecular-weight, pregnancy, risk factors, venous thromboembolism

1 | INTRODUCTION

Women who are pregnant or in the puerperium (up to 6 weeks after delivery) are at increased risk of venous thromboembolism (VTE) [1]. While VTE is uncommon, occurring at rate of 1 or 2 per 1000 deliveries [2,3], it remains the leading cause of direct maternal death in the United Kingdom (UK), with a mortality rate of 1 per 100 000 maternities [4]. In the UK, the Royal College of Obstetricians and Gynecologists (RCOG) Guideline recommends weight-adjusted low-molecular-weight heparin (LMWH) for thromboprophylaxis to prevent VTE in women at higher risk [5]. However, high-quality trials to assess the effectiveness and safety of LMWH in women who are pregnant or in the puerperium are lacking [6]. This has led to considerable variation in recommendations for VTE prophylaxis across international guidelines, with many recommendations based on research findings extrapolated from other populations, such as medical and surgical inpatients [7].

The decision to offer thromboprophylaxis involves weighing the potential benefit of VTE prevention against the potential increased bleeding risk for the individual and the cost to the healthcare system. Using an appropriate risk assessment model (RAM) to select women at higher risk of VTE for thromboprophylaxis is clearly important, as the balance of risks and harms varies according to whether a woman is at high or low risk of VTE. Various international guidelines on preventing pregnancy-associated VTE have been shown to result in differing proportions of women being offered postpartum prophylaxis, ranging from 7% to 37% [8]. In comparison, the current RCOG guidance suggests that 35% of postpartum women (without a prior VTE) would be eligible for at least 10 days of prophylaxis [1]. We do not currently know whether using an alternative RAM with a higher or lower threshold for offering prophylaxis would offer a better balance of risks, benefits, and costs. Identifying the appropriate group to receive thromboprophylaxis will depend on the effectiveness of LMWH in reducing VTE risk, which is poorly informed by the existing evidence base and could be addressed by further primary research. The value and acceptability of further primary research in women with risk factors for VTE during pregnancy and the puerperium needs to be assessed to identify groups in whom research should be prioritized.

Decision-analytic modeling is a framework in which the existing evidence is synthesized to predict the outcomes of different policies, such as determining whether using an alternative RAM would be more cost effective than the current RCOG recommendations. Expected value of perfect information (EVPI) analysis can then be used to quantify the overall uncertainty regarding the optimal thromboprophylaxis strategy. EVPI analysis can also be used to identify the specific areas of uncertainty within the existing evidence base where further primary research would be most worthwhile [9]. Expected value of sample information (EVSI) analysis can be used to estimate the value of conducting different research studies by simulating the potential outcomes of those studies and how they would be used to make better-informed decisions in the future [10]. Our aim was to use decision-analytic modeling combined with EVPI and EVSI analyses to determine whether further primary research would be worthwhile to inform UK National Health Service (NHS) practice on the appropriate provision of thromboprophylaxis for women in pregnancy and the puerperium with different risk factors [11].

2 | METHODS

2.1 | Decision problem

A decision-analytic model was developed to simulate expected lifetime costs and benefits, expressed as quality-adjusted life-years (QALYs), for women who are pregnant or in the puerperium under different thromboprophylaxis strategies. The model takes a UK NHS and personal social services perspective with future costs and benefits discounted at 3.5%. Costs are reported in pound sterling based on 2020 prices. QALYs were assumed to be valued at £30 000 when estimating EVPI and EVSI.

Antepartum women being assessed for prophylaxis were modeled separately from women being risk-assessed postpartum. The analysis for postpartum women excluded any women who qualified for antepartum prophylaxis as these women are assumed to require postpartum prophylaxis, based on the current UK guidelines. Specific populations were selected for modeling based on the availability of RAM performance estimates from a published systematic review [12]. The populations modeled were high-risk antepartum women, such as those with a prior VTE and/or thrombophilia, postpartum women with specific risk factors (obesity or cesarean delivery), and unselected postpartum women.

The strategies compared in high-risk antepartum women were RAM-based antepartum thromboprophylaxis followed by postpartum prophylaxis for all, antepartum and postpartum thromboprophylaxis for all, postpartum thromboprophylaxis for all, and no thromboprophylaxis. The RAMs considered for high-risk antepartum women were the Efficacy of Thromboprophylaxis as an Intervention during Gravidity (EThIG) and Lyon RAMs [13,14]. In high-risk antepartum women, antepartum prophylaxis was assumed to be weight-adjusted LMWH started at booking, and postpartum prophylaxis was assumed to be LMWH continued until 6 weeks postdelivery.

In each postpartum population, the strategies compared were RAM-based prophylaxis, prophylaxis for all, and prophylaxis for none. For postpartum women, prophylaxis was assumed to be weight-

adjusted LMWH given for 10 days postpartum. In the unselected postpartum population, the RAMs considered were RCOG [1,15], the Swedish Society of Obstetrics and Gynecology [1,16], Caprini [15], and the novel Sultan RAM [1]. The RAMs considered in women with risk factors were the Ellis–Kahana RAM in obese postpartum women [17] and the RCOG and Binstock RAMs in women following cesarean section [18]. Due to the low specificity of the RCOG and Binstock RAMs when used after cesarean section, we also conducted a scenario analysis assuming that a RAM was available for women following cesarean section with performance similar to the Sultan RAM in unselected women.

2.2 | Model structure

The decision-analytic model consisted of a short-term decision-tree phase followed by a lifetime state-transition model (Supplementary Figures S1 and S2). The conceptual model was developed in collaboration with clinical and patient experts who provided guidance on the selection of model outcomes based on relative importance and assessed the appropriateness of data sources and model assumptions. Discussions were also informed by considering published cost-effectiveness analyses that addressed related but not identical research questions.

The decision tree was used to estimate for each strategy: the number of women receiving thromboprophylaxis; the impact of thromboprophylaxis on VTE outcomes; treatment required for symptomatic VTE; incidence of wound hematoma; and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants. VTE outcomes included fatal and nonfatal pulmonary embolisms (PEs) and symptomatic and asymptomatic deep vein thromboses (DVTs), which were categorized as either proximal or distal. PEs and symptomatic DVTs were assumed to result in a minimum of 3 months of anticoagulant treatment, with treatment continued until at least 6 weeks postdelivery [19]. Major bleeds were considered to be those meeting the criteria proposed by the International Society on Thrombosis and Haemostasis subcommittee on the control of anticoagulation [20]. Major bleeds were separated into fatal bleeds, nonfatal intracerebral hemorrhage (ICH), and other nonfatal non-ICH major bleeds. Heparin-induced thrombocytopenia was not included in the model because there were no cases recorded in a systematic review of 2777 pregnancies [21]. Heparin-related osteoporosis was not included as an adverse event in the model because the use of LMWH in pregnancy has not been found to be associated with reduced bone mineral density [22].

For women being assessed for postpartum prophylaxis, a single decision tree captured the short-term outcomes. For women being assessed for antepartum prophylaxis, the decision-tree phase of the model was repeated to capture the antepartum and postpartum periods separately. Those patients who have experienced a symptomatic VTE or a nonfatal ICH in the antepartum model were assumed to remain in the same health state in the postpartum phase; all other patients remained at risk of VTE and progressed to the postpartum decision tree. The decision-tree phase covers a total period of 1 year, with the antepartum decision-tree covering the first 30 weeks from booking to delivery and the postpartum decision-tree covering the remaining 155 days. This was considered sufficient to cover both the period at risk of VTE (up to 6 weeks postpartum) and the 3 months required for anticoagulant treatment following VTE.

The long-term state-transition model captured the QALY losses from fatal PEs, fatal bleeds, and ongoing morbidity from ICH. It also included morbidity from chronic thromboembolic pulmonary hypertension (CTEPH) and postthrombotic syndrome (PTS), which may occur following PE and DVT, respectively. The risk of PTS was allowed to differ according to whether the DVT was proximal or distal and whether it was symptomatic and treated or asymptomatic and therefore undetected and untreated. The CTEPH health state was divided according to whether patients received medical or surgical management to allow for differential costs and survival. Further adverse outcomes were not modeled in patients who have experienced an ICH, as the lifetime costs and QALYs in these patients were assumed to be predominantly determined by the ICH-related morbidity. All-cause mortality from the decision-tree phase was applied on entry to the state-transition model. Thereafter, the state-transition model had annual cycles, with all transitions assumed to occur halfway through each cycle.

2.3 | Epidemiological parameters

Patient characteristics were based on published sources (average age of 30 years [1] and body mass index [BMI] of 36 kg/m^2 for obese postpartum women [17] and 27 kg/m^2 for others [23]). When identifying data sources for the risk of adverse outcomes in high-risk antepartum women, we focused on data sources related to women with a prior VTE. For postpartum women, we focused on data sources for women following cesarean section, as this is one of the most common reasons for offering postpartum prophylaxis [8]. However, VTE risks have been specifically estimated for each postpartum population. Data on the absolute risk of DVT, fatal PE, nonfatal PE, fatal bleeding, nonfatal major bleeding (including ICH), and wound hematoma were obtained from the literature and are summarized in Table 1, with further details provided in the supporting information [1,24–41].

The 3-year cumulative risks of PTS following antenatal DVT, distal postpartum DVT, and proximal postpartum DVT were assumed to be 34%, 31%, and 66%, respectively, based on data from Wik et al. [42], with the distribution across the 3 years based on Van Dongen et al. [43]. We assumed the same risk for asymptomatic DVTs but explored zero PTS risk for asymptomatic DVTs in a scenario analysis. The 2-year risk of CTEPH was assumed to be 3.2% based on data from a nonpregnant population [44]. Published data from nonpregnant populations were also used to estimate mortality risks following CTEPH and ICH [45,46], but the case fatality rate for PE was based on a systematic review and meta-analysis of 4 studies of pregnancy-related PE [47]. All-cause mortality from UK life tables was applied to all other health states [48].

TABLE 1 Absolute risks of VTE and bleeding for each specific population modeled[a].

	High-risk antepartum women (eg, prior VTE)		Postpartum women		
Parameter	**Antepartum**	**Postpartum**	**Unselected**	**Cesarean section**	**Obese**
Absolute risk of PE without prophylaxis, %	1.40	1.65	0.017	0.029	0.037
Absolute risk of symptomatic DVT without prophylaxis, %	4.41	5.20	0.055	0.092	0.116
Absolute risk of asymptomatic DVT without prophylaxis, %	0[b]	20.80	0.229	0.37	0.46
RR of VTE for prophylaxis (LMWH) vs no prophylaxis	0.33	0.33	0.53[c]	0.53[c]	0.53[c]
Absolute risk of major bleeding with prophylaxis (LMWH), %	0.24	5.49	4.58	4.58	4.58
RR of bleeding for prophylaxis (LMWH) vs no prophylaxis	1.53	1.53	1.53	1.53	1.53
Absolute risk of fatal major bleeding (without LMWH)	0.5 per 100 000	0.6 per 100 000	0.6 per 100 000	0.6 per 100 000	0.6 per 100 000
Absolute risk of nonfatal ICH (without LMWH)	0.9 per 100 000	1.1 per 100 000	1.1 per 100 000	1.1 per 100 000	1.1 per 100 000
Absolute increase in risk of wound hematoma for LMWH, %	NA	2.1	0.6	0.6	0.6

DVT, deep vein thrombosis; ICH, intracerebral hemorrhage; LMWH, low-molecular-weight heparin; NA, not applicable; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.

[a] Literature-based estimates with detailed sources provided in Supplementary Table S1.

[b] Risk of asymptomatic VTE is assumed to be zero in the antepartum model to ensure women remain at risk of symptomatic VTE in the postpartum model.

[c] Average over 6 weeks based on RR of 0.33 applied for 3 weeks and no efficacy thereafter.

2.4 | RAM performance data

RAM performance was estimated from a published systematic review, and the data included in the model are summarized in Figure 1. For the EThIG and Lyon RAMs, we have assumed that the RAMs are used to determine which patients should receive antepartum prophylaxis, and therefore, the data relate to the performance of these RAMs in predicting antepartum VTE [13,14]. For the Sultan RAM, performance data are available for multiple cutoff points, representing people in the top 1%, 5%, 10%, 20%, and 25% of absolute risk [1]. For the Ellis–

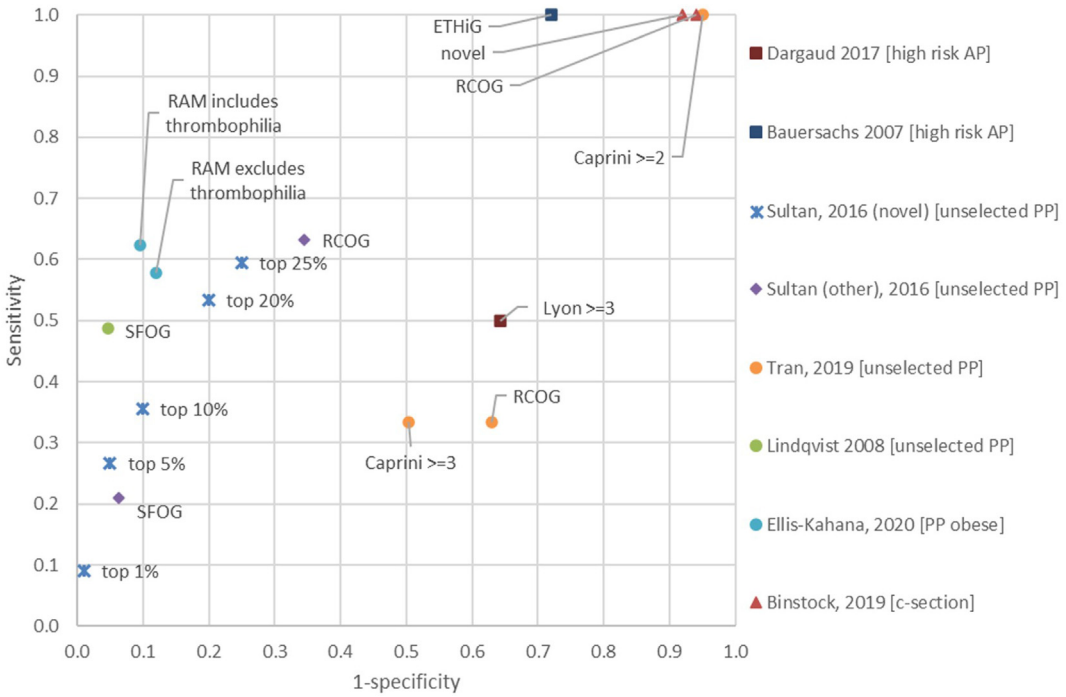

FIGURE 1 Performance of risk assessment models included in the decision analysis. AP, antepartum; ETHiG, Efficacy of Thromboprophylaxis as an Intervention during Gravidity; PP, postpartum; RAM, risk assessment model; RCOG; Royal College of Obstetricians and Gynecologists; SFOG, Swedish Society of Obstetrics and Gynecology.

Kahana RAM, 2 versions are provided based on whether thrombophilia was included or excluded from the risk algorithm, and both versions were included in the analysis [17].

2.5 | Effectiveness and safety of LMWH

An updated Cochrane review by Middleton et al. [6] was used to identify randomized controlled trials (RCTs) assessing the effectiveness of LMWH in women who are pregnant or in the puerperium. A single small pilot RCT for LMWH in antepartum women was used in the base case model as the effectiveness estimate in antepartum women (relative risk [RR], 0.33; 95% CI, 0.02-7.14) [49], as it is more directly relevant than the other antepartum trials available. This was because the remaining studies either explicitly excluded women at high risk of VTE [50,51] or used LMWH at a dose that was not consistent with the RCOG recommendations for VTE prophylaxis [52]. In the postpartum population, Middleton et al. [6] estimated a higher risk of VTE for LMWH compared with no LMWH, based on a meta-analysis of 2 small pilot RCTs. This finding was the opposite of what is expected based on studies in medical (RR, 0.49; 95% CI, 0.37-0.67) and surgical cohorts (odds ratio, 0.26; 95% CI, 0.09-0.87) [53]. We wanted the model to reflect the high uncertainty around the effectiveness of postpartum prophylaxis but did not consider it plausible to assume a higher risk of VTE with LMWH than without. Therefore, we decided to use the RR from the antepartum pilot RCT in the postpartum model. The average efficacy that can be achieved across the whole 6-week period of postpartum VTE risk by offering 10 days of LMWH is uncertain. It is possible that early postpartum prophylaxis would reduce the risk of a VTE being diagnosed in the weeks after prophylaxis is stopped because it stops clot formation in the early postpartum period. However, the period over which this reduction in VTE risk would apply is uncertain. In the base case, we assumed that LMWH given for 10 days postpartum reduced the VTE risk for the first 3 weeks (giving an effective average RR of 0.53 over the 6-week period), and this was varied from 10 days to 6 weeks in scenario analysis.

The systematic review also provided limited data on the safety of LMWH in pregnancy and the puerperium, as the only antepartum RCT reporting major bleeding (RR, 1.48; 95% CI, 0.25-8.72) used a higher dose of LMWH than is recommended by the RCOG [52]. Furthermore, the only postpartum data available were from a pilot RCT, which reported a very wide CI based on a single major bleeding event (RR, 3.53; 95% CI, 0.15-81.11) [54]. Although it is expected that the absolute risk of bleeding is likely to differ between pregnant women and general medical inpatients, it was decided that the RR of bleeding estimated from medical cohorts (RR, 1.53; 95% CI, 0.80-2.92) could be applied to women having antepartum prophylaxis [55], as the dose of LMWH used in medicalinpatients is consistent with that recommended by RCOG. Therefore, the RR from medical inpatients was applied in the base case, and scenario analyses were conducted using the midpoint RRs from the 2 studies in antepartum and postpartum women.

2.6 | Resource use and costs

Unit costs were based on standard NHS sources [56–58]. Resource use was based on published estimates and clinical expert opinion. Drug costs for LMWH as prophylaxis were based on the assumption that the lowest cost LMWH preparation would be prescribed when using prophylaxis doses recommended by RCOG [5]. As weight-based doses are recommended by RCOG, the prophylaxis dose was higher for the analysis in obese postpartum women. For treatment dose LMWH, a published survey of clinicians was used to estimate typical prescribing patterns [59]. Administration of a RAM by a hospital consultant was assumed to take 5 minutes. Women having LMWH as prophylaxis or treatment were assumed to receive training on self-administering LMWH, with district nurse administration for the small minority (4%) unable to self-inject [60]. For women having antepartum prophylaxis, 1 additional outpatient appointment was assumed late in pregnancy to discuss stopping LMWH at the onset of labor or prior to planned delivery. We assumed that women having treatment dose LMWH would have monthly joint outpatient appointments with a hematologist and obstetrician. We assumed that the average timing of antepartum VTE was 24 weeks gestation, resulting in 154 days of VTE treatment being required. Resource use assumptions for the diagnosis and management of VTE were based on published sources, including data from the UK Obstetric Surveillance System audit, supplemented with clinical expert opinion [61,62]. The costs for fatal and nonfatal ICH were based on published estimates of the cost of stroke in nonpregnant populations [63]. The cost of wound hematoma was tied to the assumption that it would increase the length of stay for delivery, resulting in a long-stay rather than a short-stay admission. A scenario analysis was also conducted, exploring an alternative assumption that wound hematoma would only lead to emergency room attendance. The cost of managing a gastrointestinal bleed in a nonpregnant population was used as a proxy for the cost of managing nonfatal non-ICH major bleeds associated with prophylaxis or treatment dose LMWH. Given the indirectness of this estimate, uncertainty around this cost was explored in scenario analysis. The cost of managing PTS and CTEPH was based on published estimates from nonpregnant populations [53,64]. The costs applied in the model are summarized in Table 2, with further details in the Supplementary Information.

2.7 | Health-related quality of life

Utility is a measure of health-related quality-of-life (HRQoL) on a scale of 0 to 1, where 1 represents full health, and 0 represents a state equivalent to death. A systematic review by Etxeandia-Ikobaltzeta et al. [65] identified one study that reported HRQoL scores for pregnancy-related VTE and major obstetric bleeding, but it did not provide data suitable for measuring utility. We therefore incorporated literature-based estimates of utility values for PE, DVT, PTS, and CTEPH [66–70], which have been applied in previous models examining the use of LMWH as prophylaxis in nonpregnant populations [53]. As Etxeandia-Ikobaltzeta et al. [65] reported similar HRQoL scores for pregnancy-associated PE and major

TABLE 2 Cost and utility parameters[a].

Parameter description	Cost	Utility
Application of RAM to patient	£9.92	NA
Thromboprophylaxis for postpartum women requiring 10 days of prophylaxis	Drug cost of £28 (£42 for the obese subgroup) Administration cost of £75	A decrement of 0.007 was applied during thromboprophylaxis
Thromboprophylaxis for high-risk antepartum women requiring prophylaxis from booking until 6 weeks	Drug cost of £711 Administration cost of £322 Monitoring cost of £205	A decrement of 0.007 was applied during thromboprophylaxis
Well patient without symptomatic VTE or major bleeding	NA	Value of 0.923 in year 1 with age adjustment thereafter
Symptomatic proximal DVT	£2092 for postnatal DVT £3300 for antenatal DVT	Value of 0.888 in the decision-tree phase Decrement of 0.011 during anticoagulant treatment Multiplier applied in a long-term model only to those having PTS
Symptomatic distal DVT	£1972 for postnatal DVT £3060 for antenatal DVT	As for symptomatic proximal DVT
Nonfatal PE	£3321 for postnatal PE £5024 for antenatal PE	Value of 0.886 in the decision-tree phase Decrement of 0.011 during anticoagulant treatment Multiplier in long-term model applied only to those having CTEPH
Fatal PE	£3117 for postnatal PE £3261 for antenatal PE	0
Fatal bleed	£1866	0
Nonfatal non-ICH bleed	£1210	Value of 0.790 for 1 month after bleed
Nonfatal ICH	£22 005 in the first 90 days £8379 per annum thereafter	Value of 0.703 in the decision-tree phase Multiplier of 0.902 thereafter
Wound hematoma	£1372	No decrement
PTS	£293 in year 1 £78 in each subsequent year	Multiplier of 0.895 in the long-term model
CTEPH medically managed	£18 980 each year	Multiplier of 0.629 in the long-term model
CTEPH surgically managed	£10 237 in year 1 and zero in year 2 onwards	Multiplier of 0.629 in the first year after CTEPH is diagnosed

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; NA, not applicable; PE, pulmonary embolism; PTS, postthrombotic syndrome; RAM, risk assessment model; VTE, venous thromboembolism.
[a] Sources described in full in the Supplementary Tables S2–S6.

obstetric bleeding, we assumed that the utility value in the month after major bleeding (other than ICH) was similar to the utility in the first month after PE [65]. To reflect the fact that people may prefer to avoid taking a treatment that requires regular injections, we included a utility decrement for people taking LMWH as either prophylaxis or treatment [71]. Utility values for patients not experiencing VTE, bleeding events, or long-term sequelae following VTE were based on general population norms, with age-related decrements applied over the individual's lifetime [72]. For DVT and PE, separate utility decrements were applied up to 1 year (ie, during the decision-tree phase) to reflect the greatest burden occurring in the acute period, with no or minimal utility decrement thereafter for DVT and PE, respectively. Utility decrements for ICH, PTS, and medically treated CTEPH were assumed to be life-long, with symptoms of CTEPH being assumed to resolve after surgery. As the disutility of PTS was not stratified by severity, we conducted a scenario analysis exploring the impact of a lower disutility for PTS (2% instead of 10%). The utility values applied in the model are summarized in Table 2, with further details provided in the Supplementary Information.

2.8 | Quantifying decision uncertainty and value of further research

Probabilistic sensitivity analysis (PSA) was conducted to incorporate the uncertainty around each model input and determine how this translates into uncertainty regarding the optimal thromboprophylaxis

strategy, which was defined as the strategy with the highest net monetary benefit (the value of the QALYs gained minus the additional costs to achieve those gains) when valuing QALYs at £30 000. The overall EVPI is an estimate of the increase in net monetary benefit that could be achieved by having perfect information on all model parameters simultaneously and is a measure of overall decision uncertainty given the current evidence [9]. The increase in net monetary benefit that can be achieved by obtaining perfect information on individual parameters or groups of parameters is known as the expected value of perfect parameter information (EVPPI) [9]. This was used to determine what research question should be addressed in future studies. EVSI was then used to simulate the potential outcomes of those future studies and how they would be used to inform future decisions regarding prophylaxis strategies [10]. As the precision of the parameters obtained from any future study will be limited by its sample size, the EVSI was conducted assuming a range of potential study sizes. The EVPPI and EVSI analyses were conducted using the Sheffield Accelerated Value of Information Analysis tool, which uses a regression-based approach to obtain value of information estimates from the PSA outputs [73,74]. We used 10 000 PSA simulations and assumed that the results of future studies would influence future care across 5 years of births in England and Wales. Full details of the parameter distributions assumed in the PSA are provided in the Supplementary Information. Scenario analyses were also used to explore aspects of structural uncertainty, such as the choice of one data source over another, and these were conducted using mean estimates for parameters (referred to as the deterministic model).

2.9 | Patient and public involvement

The project team included a patient expert member with both relevant personal experience and access to a broader group of patients through Thrombosis UK. Her attendance at team meetings ensured that patient and public values were reflected in the decision-analytic modeling throughout the process, from research design to interpretation of the findings. The project team also conducted qualitative research to assess the acceptability of future studies to patients [75], which was taken into account when identifying research priorities.

3 | RESULTS

The decision-analytic modeling identified high decision uncertainty regarding the optimal risk assessment strategy in the high-risk antepartum population (Table 3). Although a strategy of providing only postpartum prophylaxis had the highest net monetary benefit on average across the PSA samples, it only had a 36% probability of being optimal. A strategy of offering no prophylaxis had a 24% probability of being optimal, and RAM-based prophylaxis using the EThIG RAM had a 22% probability of being optimal.

In the obese postpartum population, the decision uncertainty was also high, with no prophylaxis being the optimal strategy based on average costs and QALYs estimated across the PSA samples, but RAM-based prophylaxis, using the Ellis–Kahana RAM (version including thrombophilia), having the highest probability (64%) of being the optimal strategy.

In women who have had a cesarean section, the low specificity of the RCOG and Binstock RAMs, combined with the low absolute risk of VTE, meant that a strategy of no prophylaxis was highly likely to be optimal (93% probability). There was greater decision uncertainty in the scenario analysis, assuming that a RAM was available in the cesarean section population with performance similar to the Sultan RAM in the unselected postpartum population. However, prophylaxis for none still had a 57% probability of being the optimal strategy in this scenario analysis. In the unselected postpartum population, there was low decision uncertainty due to the low absolute risk of VTE, meaning that prophylaxis for none was likely to be the optimal strategy (89% probability).

For obese postpartum women, the EVPI per person was only £22.35, but the population EVPI was high at £13.38 million over 5 years, as 129 000 births per annum are expected in this group (Table 3). For high-risk antepartum women, such as those with a prior VTE, the EVPI per person was much higher at £1453.87, reflecting the greater consequences of choosing the wrong prophylaxis strategy in women at high risk of VTE. However, the group of women known to be high-risk at booking is much smaller, with only around 3000 births per annum expected, giving a population EVPI over 5 years of births of £21.75 million in this group. The population EVPI was much lower for both women who have had cesarean section and unselected postpartum women. For both the high-risk antepartum population and the obese postpartum population, the main source of decision uncertainty was the wide CI around the RR of VTE, with the EVPPI for this individual parameter accounting for over 90% of the decision uncertainty (ie, the overall EVPI) in these 2 populations (Table 3).

Given the EVPPI findings, the EVSI analysis focused on study designs that would provide a more precise estimate of the RR of VTE for LMWH compared with no LMWH. The analysis focused on the high-risk antepartum population and the obese postpartum population based on these groups having the highest population EVPI. Figure 2 shows the EVSI for RCTs of LMWH vs no LMWH for trials of different sizes in these 2 populations. It can be seen that a trial enrolling 300 obese postpartum participants per arm would have a value of £2.8 million if the information gained from that trial were then used to make better-informed decisions regarding thromboprophylaxis over 5 years of births in England and Wales. While larger trials would have a greater value because they would provide a more precise estimate of the effectiveness of LMWH, Figure 2B shows diminishing returns as the trial size increases, reaching a ceiling value of around £12 million for a trial of 10 000 participants per arm. A smaller trial of high-risk antepartum women, enrolling only 30 participants per arm, would have a higher value of £13.1 million (Figure 2A) due to the greater decision uncertainty associated with choosing the wrong prophylaxis strategy in this high-risk group.

While the EVPI and EVSI analyses focus on the uncertainty related to the precision of the parameters used in the cost-effectiveness analysis,

TABLE 3 Decision uncertainty given current evidence.

Outcome	High-risk antepartum women (eg, prior VTE)	Postpartum women			
		Unselected	Cesarean section	Cesarean section scenario[a]	Obese
Optimal strategy given current evidence[b]	Postpartum PPX only	PPX for none	PPX for none	PPX for none	PPX for none
Probability of another strategy being optimal, %	64	11	7	43	64
EVPI per person, £	1453.87	0.68	2.06	7.74	22.35
Births per annum	3202	640 370	155 610	155 610	128 740
Population EVPI[c], £ million	21.75	2.04	1.50	5.63	13.38
Percentage of EVPI related to RR of VTE, %	94	<1	<1	68	99

EVPI, expected value of perfect information; PPX, prophylaxis; RR, relative risk; VTE, venous thromboembolism.
[a] Scenario assumes that a risk assessment model (RAM) is available with similar performance to the Sultan RAM in unselected postpartum women, whereas main results include only performance for the Royal College of Obstetricians and Gynecologists Guideline and novel RAMs reported by Binstock and Larkin [18], which had data in the relevant population.
[b] Strategy that maximizes incremental net monetary benefit when valuing a quality-adjusted life-year at £30 000.
[c] Over 5 years of births in England and Wales with future costs and quality-adjusted life-years discounted at 3.5%.

the deterministic scenario analyses explore uncertainty related to assumptions made in the model or decisions to use one data source over another to estimate a parameter. Results for the deterministic scenario analyses are provided in the Supplementary Information.

4 | DISCUSSION

The decision analysis has identified that the main source of uncertainty regarding the optimal thromboprophylaxis strategies in women who are pregnant or have recently delivered arises from a lack of high-quality trials of LMWH compared with no LMWH in these populations, with the most applicable RCT evidence coming from a small pilot study of 8 women per arm. While it was previously known that the lack of high-quality evidence on the effectiveness of LMWH to prevent VTE was contributing to uncertainty regarding the optimal prophylaxis strategy, it was unclear which groups were most affected by this uncertainty. We identified that a RCT of LMWH vs no LMWH in either high-risk antepartum women (eg, those with a prior VTE) or obese postpartum women is likely to have a higher value than a RCT in unselected postpartum women or women following cesarean section.

The main strength of this study is that it identified which weaknesses in the existing evidence base contribute most to the decision uncertainty regarding appropriate thromboprophylaxis strategies in this population. This is in contrast to the usual approach taken when synthesizing evidence to inform clinical practice guidelines, in which weaknesses in the evidence are identified and acknowledged, and then recommendations for best practice are informed by either clinical consensus or extrapolating evidence from other populations. The main limitations in our analysis relate to areas where data were lacking entirely, such as an absence of studies on the performance of the RCOG guideline in an antepartum population. In addition, while the EVPI and EVSI analyses incorporate the lack of precision around parameter estimates, they may not capture uncertainty related to study quality. For example, the performance estimates for the Ellis–Kahana RAM in obese postpartum women were derived and validated within a single cohort using a bootstrap validation approach. While this RAM lacked validation in an external study, it was included in the analysis because the methods used to develop and validate it were considered no less robust than those used for other RAMs included in the review, which had external validation studies but were not statistically derived. The EVPI/EVSI analysis also does not capture structural uncertainty, such as uncertainty regarding whether 10 days of postpartum LMWH will reduce the risk of VTE for only 10 days or whether it will reduce the risk of VTE being diagnosed up to 3 or 6 weeks later. This assumption was found to be important in the scenario analysis (see Supplementary Information). While not included in the EVPI/EVSI analysis, it would be logical to assume that the uncertainty regarding the duration of treatment effect would further support the conclusion that a RCT of postpartum LMWH would be worthwhile.

To provide some context as to whether the research benefits are likely to outweigh the research costs, an informal review of National Institute for Health and Care Research (NIHR) funded projects was conducted to identify clinical trials of pharmacological interventions in women who are pregnant or who have recently given birth. The median cost was £1.4 million with an IQR of £1.1 million to £2.0 million across 20 relevant studies, with numbers recruited ranging from 200 to 11 020 participants. This suggests that a RCT in obese postpartum women would provide value compared to typical research costs if it recruited over 300 women per arm, and a RCT in high-risk antepartum women would provide substantial value even if it recruited smaller numbers.

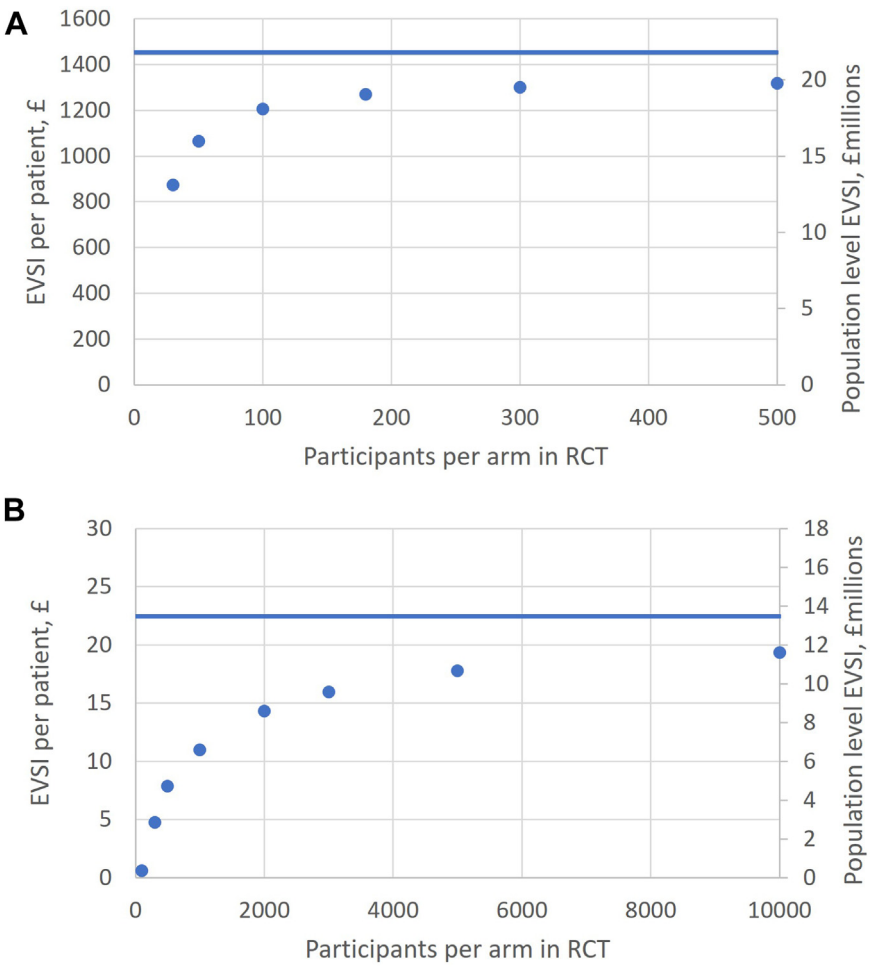

FIGURE 2 Expected value of sample information for a randomized controlled trial (RCT) of low-molecular-weight heparin vs no low-molecular-weight heparin in high-risk antepartum women (A) and obese postpartum women (B). EVSI, expected value of sample information.

However, this information should not be acted on in isolation. Qualitative research has identified that trials that randomize high-risk antepartum women with a prior VTE to placebo or no prophylaxis are unlikely to be acceptable to both the participants being recruited and their clinicians [75]. Therefore, future trials should focus on recruiting women with other risk factors. Obesity is a highly suitable risk factor to study due to its current high prevalence and easy identification. The qualitative research also suggested that clinicians would be less willing to randomize women with a BMI > 40 kg/m^2 and those having an emergency cesarean section and would be more willing to randomize women who had 2 of the following risk factors: elective cesarean section, age over 35, and obesity (30-40 kg/m^2) [75]. Pilot studies may also help in assessing the feasibility of recruiting particular groups into RCTs. Several such studies on ClinicalTrials.gov may provide valuable insights when results become available (PP-HEP [NCT05878899]; Pilot PARTUM [NCT04153760]; and LEAP [NCT05058924]).

It is acknowledged that with an expected VTE risk without prophylaxis of only 0.15% for obese postpartum women, a much larger trial of around 36 000 participants per arm would be needed to detect a difference in VTE risk of 0.07%, with 80% power and a 2-sided significance level of 5%. However, our analysis demonstrates that a much smaller trial of 300 participants per arm would have substantial value if decision-makers would be willing to use the estimates of effectiveness obtained to make better-informed decisions about prophylaxis in this population without requiring them to meet a formal statistical hypothesis test. Current guidance is based on very limited RCT evidence and an assumption that the clinical effectiveness of LMWH in women who are pregnant or in the puerperium would be similar to the effectiveness observed in nonpregnant cohorts. Therefore, clinicians are currently offering thromboprophylaxis to a substantial proportion of postpartum women without the effectiveness of LMWH in postpartum women having been demonstrated in an adequately powered study.

We conclude that future research should focus on estimating the effectiveness of thromboprophylaxis in women at risk of VTE during pregnancy and the puerperium. A clinical trial randomizing obese postpartum women to LMWH or no LMWH is expected to have substantial value. Although a trial in high-risk antepartum women, such as those who have had a previous VTE, is also expected to have substantial value, a trial recruiting obese postpartum women (ie, BMI 30-40 kg/m^2) with an additional risk factor for VTE would be more acceptable.

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AUTHOR CONTRIBUTIONS

S.D. developed the decision-analytic model and conducted the cost-effectiveness analysis. A.P. conducted the systematic review of RAMs that informed the modeling. F.S. conducted the qualitative research that informed the interpretation of the results. J.H. provided statistical support. C.N-P., B.J.H., J.D., and S.G. were members of the expert clinical group that informed the development of the decision-analytic model. All named authors contributed to the design of the study, acquisition of data, or analysis and interpretation of data, in addition to drafting/redrafting and approval of the final version of the paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DECLARATION OF COMPETING INTERESTS

All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare that the research described was conducted as part of a wider project funded by the NIHR Health Technology Assessment (NIHR HTA) program (project number NIHR131021). S.G. is chair of the NIHR HTA Clinical Trials Unit Standing Advisory Committee, is a member of the NIHR HTA Programme Oversight Committee 2009-2023, and has been a member of a number of NIHR Committees from 2009 to 2022. B.J.H. was previously involved in developing relevant National Institute for Health and Care Excellence guidance on the prevention and management of venous thromboembolic disease, is a founder and a trustee of Thrombosis UK, and was a previous Chair of the Steering Group of World Thrombosis Day. C.N-P. reports personal fees from Sanofi and UCB, and was the lead developer of the RCOG Green Top Guideline on thromboprophylaxis in pregnancy (37a). J.D. was an author on RCOG's COVID-19 guidance; no other relationships or activities could appear to have influenced the submitted work.

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SUPPLEMENTARY MATERIAL

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