Thromboprophylaxis during pregnancy and the puerperium: a systematic review and economic evaluation to estimate the value of future research

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Primary conflicts of interest: Professor Steve Goodacre is chair of the NIHR HTA Clinical Trials Unit Standing Advisory Committee, is a member of the NIHR HTA Programme Oversight Committee 2009–23 and has been a member of a number of NIHR Committees from 2009 to 2022. Professor Beverley Hunt was previously involved in developing relevant National Institute for Health and Care Excellence (NICE) guidance on prevention and management of venous thromboembolic disease and is Medical Director of Thrombosis UK and Chair of the Steering Group of World Thrombosis Day. Catherine Nelson-Piercy reports personal fees from Sanofi and UCB, and was the lead developer of the Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guideline on thromboprophylaxis in pregnancy (37a). Jahnavi Daru was an author on RCOG's COVID-19 guidance. All other authors declare no competing interests.

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Scientific summary

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Background

Pharmacological prophylaxis to prevent venous thromboembolism (VTE) is currently recommended for women who are deemed to be at high risk of VTE during pregnancy or in the 6 weeks after delivery (the puerperium). The decision to provide prophylaxis involves weighing the benefits, harms and costs, which will vary according to the individual's VTE risk. It is unclear whether the current risk stratification approach could be improved by further research.

Aims and objectives

The aim of this research was to determine whether further primary research is worthwhile to inform NHS practice on the use of risk assessment models (RAMs) for the prediction of VTE and appropriate provision of thromboprophylaxis for women in pregnancy and in the puerperium. The specific objectives were:

1. to estimate the expected costs and health benefits of providing thromboprophylaxis using current and alternative RAMs and quantify decision uncertainty
2. to determine which factors are the most important drivers of uncertainty when trying to determine the optimal risk-based thromboprophylaxis strategy
3. to identify one or more potential future studies that would reduce the current decision uncertainty, while being feasible and acceptable to patients and clinicians
4. to evaluate the value of future research studies in terms of the net health benefits to patients and the cost of the research.

Methods

To identify all relevant RAMs and their predictive performance, we undertook a systematic review in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. Systematic searches were performed across five electronic databases, including MEDLINE, EMBASE and the Cochrane Library, from inception to February 2021. We included all primary validation studies that examined the comparative accuracy of a multivariable RAM (or scoring system) for predicting the risk of developing VTE in women who are pregnant or in the puerperium. Two or more reviewers independently undertook study selection, data extraction and risk of bias assessments using the Prediction model Risk Of Bias ASsessment Tool (PROBAST). We used narrative synthesis to summarise the findings.

A decision-analytic model was used to estimate lifetime expected costs and quality-adjusted life-years (QALYs) under alternative thromboprophylaxis strategies. The decision-analytic modelling focused on the following subgroups for which data were available on the performance of RAMs:

- high-risk antepartum women (e.g. prior VTE or known thrombophilia)
- unselected postpartum women
- obese postpartum women
- postpartum women following caesarean section.

In the analysis for high-risk antepartum women, the strategies compared were:

- antepartum and postpartum prophylaxis for all (from booking to 6 weeks postpartum)
- antepartum prophylaxis according to a RAM followed by 6 weeks postpartum prophylaxis for all
- six weeks postpartum prophylaxis for all
- no prophylaxis.

In the analyses for postpartum women, the strategies compared were:

- postpartum prophylaxis for all (10 days)
- postpartum prophylaxis according to a RAM (10 days)
- no prophylaxis.

In all cases, the thromboprophylaxis agent was assumed to be low-molecular-weight heparin (LMWH). In high-risk antepartum women, the RAMs compared were the Lyon RAM and the Efficacy of Thromboprophylaxis as an Intervention during Gravidity (EThIG) RAM. For the unselected postpartum population, the RAMs compared were Royal College of Obstetricians and Gynaecologists (RCOG), Swedish Society of Obstetrics and Gynecology (SFOG), Caprini and the novel Sultan RAM. In the subgroup of obese postpartum women, the only RAM included was the novel Ellis-Kahana RAM. In the subgroup of postpartum women following caesarean section, the RAMs compared were RCOG and the novel Binstock RAM. We also conducted an analysis assuming that a RAM was available for the post-caesarean section population with performance similar to the Sultan RAM in the unselected postpartum population.

The model takes a United Kingdom (UK) NHS and Personal Social Services perspective with future costs and QALYs discounted at 3.5% per annum. Costs are reported in Great British pounds based on 2020 prices. Short-term outcomes are captured in a decision-tree phase and long-term outcomes in a lifetime state-transition model.

The decision tree is used to estimate for each strategy: the number of women receiving thromboprophylaxis; the impact of thromboprophylaxis on VTE outcomes (fatal and non-fatal pulmonary embolisms and deep-vein thromboses); and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants and wound haematoma. Major bleeds are separated into fatal bleeds, non-fatal intracerebral haemorrhages (ICH) and other major bleeds. Symptomatic VTEs are assumed to result in 3 months of anticoagulant treatment which should be continued until at least 6 weeks post delivery. Outcomes captured in the long-term model include post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension. These are in addition to the long-term model capturing the QALY losses from fatalities and ongoing morbidity from ICH.

For women being assessed for postpartum prophylaxis, a single decision tree captures the short-term outcomes. For women being assessed for antepartum prophylaxis, the decision-tree phase of the model is repeated to capture the antepartum and postpartum periods separately. Those patients who have experienced a symptomatic VTE or a non-fatal ICH in the antepartum model are assumed to remain in the same health state in the postpartum phase; all other patients remain at risk of VTE and progress to the postpartum decision tree.

All model parameters were based on published literature or clinical opinion where published evidence was lacking. Sources specific to the target population were identified for the following parameters: data related to population characteristics [age, body mass index (BMI) and life expectancy]; absolute risks of VTE, bleeding and PTS; costs of prophylaxis and VTE treatment. There is a paucity of data on the efficacy of thromboprophylaxis during pregnancy and in the puerperium. Based on the clinical expert's understanding of the mechanism of action of prophylaxis, their personal experience and the prothrombotic physiologic changes during pregnancy, it was decided that the relative risk (RR) for VTE

should be based on a single small pilot trial in antepartum women with prior VTE, while the RR for bleeding should be extrapolated from studies in medical inpatients. Other data were generally based on sources used in a published cost-effectiveness analysis of thromboprophylaxis in hospitalised patients (who are not pregnant or in the puerperium), with costs updated to reflect changes in prices. Parameter uncertainty was incorporated using probabilistic sensitivity analysis and structural uncertainty was explored using deterministic scenario analysis.

Expected value of perfect information (EVPI) analysis was used to identify the key drivers of decision uncertainty that could be reduced by future studies. We held workshops with women with a prior VTE or who had been offered thromboprophylaxis during pregnancy, and undertook a survey of healthcare professionals, to understand whether potential future trials would be acceptable to the individuals who would be invited to take part. Expected value of sample information (EVSI) analysis was then used to estimate the value of these potential future research studies.

Results

Our systematic review of RAMs included 17 studies, comprising 19 unique externally validated RAMs and 1 internally validated model (Ellis-Kahana). Estimates of sensitivity were highly variable ranging from 0% to 100% for RAMs that were applied to antepartum women and 0% to 100% for RAMs applied to postpartum women. Specificity estimates were similarly diverse ranging from 28% to 98% and 5% to 100%, respectively. Most studies had unclear or high risk of bias and applicability concerns, mainly due to limitations in participant selection and statistical analysis.

In the decision analysis for high-risk antepartum women, using the EThIG RAM to select patients for antepartum prophylaxis had a 42% probability of having an incremental cost-effectiveness ratio (ICER) under £30,000 per QALY compared to a strategy of offering only postpartum prophylaxis. This led to considerable decision uncertainty, with an overall EVPI of £1454 per patient for high-risk antepartum women, equivalent to £21.8 million over 5 years of births. A high proportion of this (94%) was related to uncertainty in the effectiveness of LWMH to reduce VTE risk compared to no prophylaxis. The EVSI analysis found that a randomised controlled trial (RCT) of 30 patients per arm comparing LMWH with no prophylaxis would have a value of £13.1 million over 5 years of births, rising to £19.7 million for a RCT of 500 patients per arm. Small trials such as these would have substantial value compared to the typical cost of trials in these populations (£1.1–2.0 million), assuming decision-makers are willing to use the estimates of efficacy obtained, to make better informed decisions about prophylaxis in this population, without requiring them to meet a formal hypothesis test.

In the decision analysis for unselected postpartum women, the poor performance of the available RAMs (including RCOG, SFOG and Sultan), combined with the relatively low absolute risk of VTE, meant that a strategy of offering no prophylaxis had an 89% probability of being optimal, when valuing a QALY at £30,000. This was reflected in an EVPI of £0.68 per person; £2.0 million over 5 years of births. No EVSI was conducted for this population due to the low EVPI estimates.

In the decision analysis for obese postpartum women, there was substantial decision uncertainty, with the Ellis-Kahana RAM having a 64% probability of being the optimal strategy when valuing a QALY at £30,000, despite the fact that on average it had lower QALYs and higher costs than a strategy of offering no prophylaxis. The overall EVPI was £22.35 per patient, or £13.4 million across 5 years of births, with a high proportion (99%) being related to the RR of VTE. The EVSI analysis found that a RCT of LMWH versus no prophylaxis in obese postpartum women would have a value of £2.8 million, over 5 years of births, if it enrolled 300 patients per arm, rising to £11.6 million if enrolling 10,000 patients per arm.

In the decision analysis for postpartum women following caesarean section, neither of the RAMs that had been specifically validated in women following caesarean section (RCOG and Binstock) performed

sufficiently well to have an ICER under £30,000 per QALY compared to a strategy of offering no prophylaxis. Offering no prophylaxis had the highest probability of being the optimal strategy (when valuing a QALY at £30,000) even when assuming that a RAM could be identified for the post-caesarean section group which performed similarly to the Sultan RAM in the unselected cohort. In this scenario, the EVPI was £7.74 per patient, equivalent to £5.6 million over 5 years of births and 68% of the overall EVPI was related to the RR of VTE. In the post-caesarean section group, a RCT of 5000 patients per arm would be needed to generate an EVSI of £2.2 million over 5 years of births, when assuming that a RAM is available which performs similarly to the Sultan RAM.

The only RAM validated in an unselected antepartum population had poor performance; therefore, analysis in this group was limited to an exploratory analysis which suggested that for a RAM to be cost-effective for use in an unselected antepartum population, it would need to have high specificity (90–95% for a sensitivity of 100–53%). Exploratory analyses were also conducted for women with three antepartum risk factors. This found that offering antepartum prophylaxis from 28 weeks to women with three antepartum risk factors (excluding prior VTE) as per current RCOG guidance is unlikely to have an ICER under £30,000 per QALY. However, a formal analysis of EVPI could not be conducted as the absolute risk in this group is not well quantified.

The workshops indicated that a study randomising women to LMWH or placebo would be less acceptable to women who have had a prior VTE or thrombophilia than for other groups of women. Surveyed healthcare professionals reported lower clinical equipoise for women with prior VTE, thrombophilia or BMI > 40 kg/m^2. The survey also suggests that healthcare professionals have greater clinical equipoise for a study determining the effectiveness of thromboprophylaxis in antepartum women with three clinical risk factors (other than prior VTE or thrombophilia) who are currently eligible for prophylaxis from 28 weeks. The survey results also suggest that in postpartum women there is greater clinical equipoise in women whose risk factors are an elective caesarean section combined with either age over 35 years or obesity, and women whose only clinical risk factors are age and a BMI between 30 and 40 kg/m^2. Workshop participants reported receiving limited information about VTE or risks and benefits of thromboprophylaxis during pregnancy and the puerperium and those without prior VTE often did not understand why they had received treatment. However, women with experience of a prior VTE felt that it would not be ethical to randomise women to placebo given the perceived risk of VTE and the perceived effectiveness of LMWH in this group. Although the workshop participants generally favoured cluster randomisation over individual randomisation, clinicians felt individual randomisation was more acceptable.

Conclusions

The benefits of thromboprophylaxis clearly outweigh the risks in those with the highest risk of VTE, such as women with a prior VTE, but the balance of benefits and harms is less clear in lower-risk groups. There is substantial decision uncertainty regarding the use of RAMs to select high-risk women for antepartum prophylaxis and obese postpartum women for postpartum prophylaxis. The main source of decision uncertainty was related to the RR reduction of thromboprophylaxis for preventing VTE due to a lack of RCTs in pregnancy and the puerperium. This uncertainty is reflected in the widely variant strategies and guidelines for use of thromboprophylaxis in obstetric populations in different countries, notably the USA and UK. The expected benefits of conducting further trials to reduce this uncertainty are highly relative to typical research costs, but in the UK, clinical trials are more likely to be acceptable and feasible in the group of women who have not had a previous VTE. In unselected postpartum women and women following caesarean section, the poor performance of available RAMs (including RCOG) meant that RAM-based prophylaxis strategies had less favourable cost-effectiveness with lower decision uncertainty.

Recommendations for future research

Future research should focus on estimating the efficacy of thromboprophylaxis in preventing VTE in pregnancy and the puerperium. Clinical trials comparing LMWH with no prophylaxis would be more acceptable to both healthcare professionals and the public, in women who have not had a previous VTE, but who have other risk factors, such as obesity.

Study registration

This study is registered as PROSPERO CRD42020221094.

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