Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study

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Executive summary

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Background

Thrombophilia is a recognised risk factor for venous thromboembolism (VTE). However, the optimal management is unclear in terms of the need for and effectiveness of antithrombotic interventions, especially in high-risk patient groups, including the use of oral oestrogen preparations, pregnancy and major orthopaedic surgery. Clinicians have come under pressure to initiate thrombophilia testing on an increasing number of patients and thrombophilia screening in selected patient groups has been suggested.

Objectives

The objectives of this study were as follows:

- To assess the risk of clinical complications associated with thrombophilia in three high-risk patient groups: (1) women who are prescribed oral oestrogen preparations, (2) pregnancy and the puerperium and (3) patients undergoing major orthopaedic surgery.
- To assess the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia, undergoing major orthopaedic surgery.
- To evaluate the relative cost-effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening. Four screening scenarios were assessed: (1) testing women prior to prescribing combined oral contraceptives and restricting prescribing to those tested negative for thrombophilia; (2) testing women prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia; (3) testing women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia; and (4) testing all patients prior to major elective orthopaedic surgery and prescribing extended thromboprophylaxis to those tested positive for thrombophilia.

Methods

Risk of clinical complications

Systematic review and meta-analyses were conducted to establish the risk of clinical complications associated with thrombophilia in women who use oral oestrogen therapy, women who are pregnant and patients undergoing major orthopaedic surgery.

Data sources

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia, oral oestrogen, pregnancy and orthopaedic surgery were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out.

Review methods

All prospective and retrospective studies of VTE events and thrombophilia in women taking oral oestrogen preparations and patients undergoing major orthopaedic surgery and studies of VTE events and adverse obstetric complications in women with thrombophilia during pregnancy were considered. Only relevant studies that reported categorical data relating to the presence and absence of thrombophilia were included. Data were extracted into prepiloted data extraction forms and the methodological quality of the studies was assessed based on a seven-criterion checklist. Odds ratios (ORs) associated with individual clinical outcomes, stratified by thrombophilia type, were calculated for each patient group. Meta-analysis was conducted.
based on the random effects model. Testing of heterogeneity was carried out with the standard \( \chi^2 \) test.

**The effectiveness of prophylaxis**

Systematic review and meta-analyses were conducted to assess the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy and VTE events in patients with thrombophilia, undergoing major orthopaedic surgery.

**Data sources**

All major electronic databases were searched by two independent reviewers: MEDLINE 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, the Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia pregnancy, and orthopaedic surgery were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out.

**Review methods**

All prospective and retrospective studies containing data on the use of all types of prophylaxis in the prevention of VTE and pregnancy loss in women with thrombophilic defects who are pregnant and the use of thromboprophylaxis in the prevention of VTE in patients with thrombophilia undergoing major elective orthopaedic surgery were considered. Only relevant studies that reported categorical data relating to the presence and absence of thrombophilia, and orthopaedic surgery were used to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Handsearching of the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out. Data were extracted into prepiloted data extraction forms and the methodological quality of the studies was assessed based on a seven-criterion checklist. These were summarised according to the patient groups and stratified according to the types of prophylaxis. A narrative summary was provided; where appropriate, meta-analysis was conducted based on the random effects model. Testing of heterogeneity was carried out with the standard \( \chi^2 \) test.

**Cost-effectiveness analysis**

An incremental cost-effectiveness analysis was conducted, from the perspective of the NHS in the UK, to determine the relative cost-effectiveness in universal and selective, history-based screening for thrombophilia in these patient groups. A decision analytical model was developed to simulate the clinical consequences of four thrombophilia screening scenarios: screening women prior to prescribing combined oral contraceptives, screening women prior to prescribing hormone replacement therapy, screening women at the onset of pregnancy (week six of gestation) and screening patients prior to major orthopaedic surgery. The probabilities of individual clinical events were derived from the meta-analyses and information from the literature. Healthcare resource use was determined by two Delphi studies of clinical management of VTE and adverse pregnancy complications. Only direct health service costs were measured and unit costs for all healthcare resources used were obtained from routinely collected data and the literature. Cost-effectiveness was expressed as incremental cost-effectiveness ratios (ICERs). The ICERs, which were presented as costs per adverse clinical complication prevented when comparing universal and selected screening with no screening, were calculated for each patient group.

**Results**

**Risk of clinical complications**

Of all the studies identified from the search, 201 related to oral oestrogen preparation, 234 to pregnancy and 149 to orthopaedic surgery. Overall, 81 studies were included in the review, nine for oral oestrogen preparations, 72 for pregnancy and eight for orthopaedic surgery. Reasons for exclusion included inappropriate study type (such as reviews, and editorials), inappropriate study population, no categorical measure of the presence or absence of thrombophilia and inappropriate clinical outcomes.

**Oral oestrogen preparations**

The highest risk of VTE in oral contraceptive users was observed in women with factor V Leiden (FVL), with an OR of 15.62 [95% confidence interval (CI) 8.66 to 28.15] calculated. Deficiencies of antithrombin (OR 12.60; 95% CI 1.37 to 115.79), protein C (OR 6.33; 95% CI 1.68 to 23.87) or protein S (OR 4.88; 95% CI 1.39 to 17.10) and elevated levels of factor VIIIc (OR 8.80) were also significantly associated with venous thromboembolism in oral
contraceptive use. For hormone replacement therapy, a significant association was found in women with FVL (OR 13.16; 95% CI 4.28 to 40.47).

**Pregnancy**
The highest risk in pregnancy was found for FVL and VTE. Results of the meta-analysis suggested that homozygous carriers of this mutation are 34 times more likely to develop VTE in pregnancy than non-carriers of the mutation. Significant risks for individual thrombophilic defects were also established for early pregnancy loss (ORs ranging from 2.49; 95% CI 1.24 to 5.00 observed with prothrombin G20210A to 6.25; 95% CI 1.37 to 28.42 observed with hyperhomocysteinaemia); recurrent pregnancy loss (ORs ranging from 1.91; 95% CI 1.01 to 3.61 observed with FVL to 2.70; 95% CI 1.37 to 5.35 observed with prothrombin G20210A); late pregnancy loss (ORs ranging from 2.06; 95% CI 1.10 to 3.86 observed with FVL to 20.09; 95% CI 3.70 to 109.15 observed with protein S deficiency); preeclampsia (ORs ranging from 1.32; 95% CI 1.05 to 1.66 observed with methylene tetrahydrofolate reductase (MTHFR) to 3.49; 95% CI 1.21 to 10.11 observed with hyperhomocysteinaemia); placental abruption (ORs ranging from 4.26; 95% CI 1.63 to 11.12 observed with hyperhomocysteinaemia to 7.71; 95% CI 3.01 to 19.76 observed with prothrombin G20210A) and intrauterine growth restriction (IUGR) (ORs ranging from 2.91; 95% CI 1.13 to 7.54 observed with prothrombin G20210A to 15.20; 95% CI 1.32 to 174.96 observed with homozygous FVL).

**Orthopaedic surgery**
Significant associations were found between FVL (OR 1.86; 95% CI 1.27 to 2.74) and high factor VIIIc (OR 1.65; 95% CI 1.06 to 2.58) and postoperative VTE following elective hip or knee replacement surgery. Prothrombin G20210A was significantly associated with postoperative pulmonary embolism (OR 9.14; 95% CI 2.27 to 36.89). However, antithrombin deficiency, MTHFR and hyperhomocysteinaemia were not associated with increased risk of postoperative venous thromboembolism.

**The effectiveness of prophylaxis**
Of all the studies identified from the search, eight studies evaluated the effectiveness of prophylactic interventions in pregnant women with thrombophilia. Low-dose aspirin and heparin was the most effective in preventing pregnancy loss in thrombophilic women during pregnancy (OR 1.62; 95% CI 0.51 to 5.10), whereas aspirin alone was the most effective in preventing minor bleeding (OR 1.68; 95% CI 0.38 to 7.39). However, there were insufficient data to demonstrate statistically significant associations.

All the studies on thrombophilia and major elective orthopaedic surgery included in the review of risk complications were also used in the review of the effectiveness of thromboprophylaxis. However, there were insufficient data to determine the relative effectiveness of different thromboprophylaxis in preventing VTE in this patient group.

**Cost-effectiveness analysis**
Based on a hypothetical model of 10,000 patients in each screening scenario, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on combined oral contraceptives, 104 women on hormone replacement therapy, 2921 pregnant women and 1265 patients undergoing major orthopaedic surgery, at costs of £119,147, £1,185,428, £513,591 and £1,217,935, respectively.

When taking effectiveness of screening into account, universal screening of patients prior to prescribing hormone replacement therapy and restricting prescribing to those tested negative for thrombophilia would prevent 42 VTE events in this hypothetical population and was the most cost-effective screening strategy (ICER £6824). In contrast, screening women prior to prescribing combined oral contraceptives would only prevent three VTE events and was the least cost-effective strategy (ICER £200,402).

Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost-effective than universal screening in all four screening scenarios.

**Conclusions**

**Implications for healthcare**
Thrombophilia is associated with increased risks of VTE in women taking oral oestrogen preparations and patients undergoing major elective orthopaedic surgery, and VTE and adverse pregnancy outcomes in pregnancy. There is considerable difference in the magnitude of the risks among different patient groups with different thrombophilic defects.
In women who are on combined oral contraceptives, the ORs of VTE among those who are carriers of the FVL mutation was 15.62. However, in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low.

Significant risks for VTE and adverse pregnancy outcomes have been established with individual thrombophilic defects.

Thrombophilic defects including FVL, high plasma factor VIIIc levels and prothrombin G20210A are associated with the occurrence of postoperative VTE in elective hip or knee replacement therapy. These associations are observed in patients who were given preoperative thromboprophylaxis and are, therefore, of clinical significance.

Universal thrombophilia screening in women prior to prescribing oral oestrogen preparations, in women during pregnancy and in patients undergoing major orthopaedic surgery is not supported by the evidence. The findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening.

**Recommendations for research**

- Large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with venous thromboembolism among hormone users and in patients undergoing orthopaedic surgery.
- The relative value of a thrombophilia screening programme to other healthcare programmes needs to be established.

**Publication**

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 01/04/03. The contractual start date was in July 2002. The draft report began editorial review in March 2004 and was accepted for publication in September 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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