UK National Screening Committee

Neonatal and general adult populations screening for thrombophilia

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Final

Solutions for Public Health

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://legacy.screening.nhs.uk/screening-recommendations.php and the policy review process is described in detail at https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process

Abbreviations List

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PPV	Positive Predictive Value
UK	United Kingdom
UK NSC	UK National Screening Committee

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from Public Health England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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Plain English Summary

Thrombophilia increases an individual's risk of forming a blood clot. This can block the flow of blood through a blood vessel. The clot may block the blood vessel where it develops or break off and travel around the body with a risk of blocking blood flow (and oxygen) in an organ such as the heart, lungs or brain. This can result in events such as a stroke, heart attack, deep vein thrombosis or complications during pregnancy and childbirth.

Thrombophilia may develop in association with other diseases (eg cancer, autoimmune diseases), drug exposure (eg oral contraceptives) or condition (eg pregnancy). Babies can also inherit thrombophilia from their parents.

The UK National Screening Committee published a review on screening for thrombophilia in pregnancy in 2010. The 2010 review did not discuss the evidence on potential screening pathways or effective interventions for screening for thrombophilia in newborn babies or adults.

The aim of this review is to assess if there is enough evidence to evaluate screening for thrombophilia in newborn babies or adults. It looked at evidence published between 1946 and August 2016. This review considered these key questions:

1. What is the reported performance of screening strategies for detecting thrombophilia in neonates and adults?

2. What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

This review did not find any relevant evidence to answer these questions.

As the questions could not be answered, the review concluded that there is not enough evidence to evaluate screening for thrombophilia in newborn babies or adults.

Executive Summary

This document reviews evidence published between 1946 and August 2016 on screening for thrombophilia in neonates and adults

Background

Thrombophilia describes a number of variants that increase an individual's risk of thrombosis; the formation of a blood clot which obstructs the flow of blood. It can lead to thrombotic incidents such as stroke, myocardial infarction, deep vein thrombosis or obstetric complications. Thrombophilia can be acquired or inherited. Acquired thrombophilia is associated with another disease (eg cancer, autoimmune diseases), drug exposure (eg oral contraceptives) or condition (eg pregnancy). Inherited thrombophilia arises from inherited deficiencies or abnormalities, the most common of which effect the natural inhibitor proteins of the coagulation system. Inherited abnormalities can also relate to a deficiency of proteins that break down blood clots in the fibrinolytic system.

Previous findings

A 2010 UK National Screening Committee (UK NSC) review considered antenatal screening for thrombophilia. The current UK NSC policy is that systematic population screening for thrombophilia in pregnancy, newborns and adults is not recommended. The 2010 review did not discuss the evidence on potential screening pathways or effective interventions for screening for thrombophilia in newborn babies or adults.

The current review

The aim of this review is to evaluate if there is a body of evidence of sufficient volume and quality to justify undertaking a sustained evaluation of screening for thrombophilia in neonates and/or adults. It looks at evidence published between 1946 and August 2016.

The key questions considered in this review are:

- What is the reported performance of screening strategies for detecting thrombophilia in neonates and adults?
- What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

This review did not find any relevant evidence to answer these questions.

Recommendation

The review concluded that there is not enough evidence to evaluate screening for thrombophilia in newborn babies or adults.

Introduction

Thrombophilia describes a number of variants that increase an individual's risk of thrombosis. Thrombosis is the formation of a blood clot which obstructs the flow of blood[1]. It can lead to thrombotic events such as stroke, myocardial infarction, deep vein thrombosis or obstetric complications[2]. Thrombophilia can be acquired or inherited. Acquired thrombophilia is associated with another disease (eg cancer, autoimmune diseases), drug exposure (eg oral contraceptives) or condition (eg pregnancy). Inherited thrombophilia arises from inherited deficiencies or abnormalities, the most common of which effect the natural inhibitor proteins of the coagulation system. Inherited abnormalities can also relate to a deficiency of proteins that break down blood clots in the fibrinolytic system, however these are very rare and not tested for[1].

Clinical practice guidelines for the diagnosis and management of venous thromboembolic disease in adults and the role of thrombophilia testing are available from the National Institute for Health and Care Excellence[3].

There are a range of tests for thrombophilia including testing for antithrombin deficiency, protein C or protein S deficiencies, Factor V Leiden mutation, prothrombin gene mutation (G-20210-A) and anti-phospholipid antibodies[1].

Basis for current recommendation

The current UK National Screening Committee (UK NSC) policy is that systematic population screening for thrombophilia in pregnancy, newborns and adults is not recommended. A 2010 UK NSC review considered antenatal screening for thrombophilia[4]. The 2010 review also noted that there was no evidence for screening neonates, even in a highly selected subgroup of neonates with a first-degree relative with symptomatic inherited thrombophilia[4]. However, the search for the 2010 review was primarily directed towards thrombophilia in pregnancy[1]. The 2010 review also noted that age-specific reference ranges would be needed to interpret the results of neonatal screening for thrombophilia[4].

The 2010 UK NSC review noted that neonatal and general adult populations are at lower risk of thrombotic events than pregnant women and other high risk groups but did not discuss the available evidence on potential screening pathways or effective interventions for screening for thrombophilia in neonates and/ or adults.

Current update review and approach taken

The aim of this review is to evaluate if there is a body of evidence of sufficient volume and quality to justify undertaking a more comprehensive evaluation of screening for thrombophilia in neonates and/or adults. It was prepared by Solutions for Public Health, in discussion with the UK NSC.

The current evidence summary was developed using a rapid review methodology and assessed using the UK NSC reporting checklist for evidence summaries. The key questions addressed in the current review were developed by the UK NSC and consider the performance of screening strategies for detecting thrombophilia and the reported effectiveness of thromboprophylaxis in screen-detected populations. The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

Systematic scoping literature searches of Medline were conducted by the UK NSC on 19th August 2016 for evidence published since 1946. One search considered adult screening for thrombophilia and the second considered newborn screening for thrombophilia. A third

general search was carried out to ensure potentially relevant references were not missed. A total of 374 references were identified, including 133 references from the search on adult screening; 83 references from the search on newborn screening and 108 references from the general search. These were briefly sifted by title by the UK NSC to remove obviously irrelevant references. Details of the search terms and a flow diagram summarising the references identified are presented in the Search Strategy section at the end of this report. One hundred and forty-two references were sent to Solutions for Public Health for further appraisal and possible inclusion in the final review, including 77 references from the search on adult screening; 56 references from the search on newborn screening and 9 references from the general search. Selection and appraisal of studies was undertaken by one reviewer. Any queries were resolved through discussion with a second reviewer or with the UK NSC.

Overall, 20 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. This includes papers where relevance could not be determined from the title or abstract alone. Of these, 12 related to screening adults and 8 related to newborn screening. Studies excluded at the abstract stage concerned testing for thrombophilia in populations with known conditions such as cardiac conditions or localized scleroderma, the early development of tests, the management of patients after a thrombotic event, the cost-effectiveness of screening women for thrombophilia prior to oral contraceptive use (an excluded population in this review) and testing neonates with known or suspected health conditions. General discussion papers were also excluded.

Each section below provides information on the evidence selection process and number of included studies for the given criterion.

The review was quality assured by a second senior reviewer who was not involved with the writing of the review in accordance with Solutions for Public Health's quality assurance process.

Table 1: Key questions for current review of Neonatal and general adult populations screening for thrombophilia

Criterion*	Key Questions	# Studies Included
4. There should be a simple, safe, precise and validated screening test.	What is the reported performance of screening strategies for detecting thrombophilia in neonates and adults?	0
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.		
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?	0

* UK NSC evidence review criteria (January 2016)

Appraisal against UK NSC Criteria[†]

Each of the key questions and their associated criteria are considered in turn below.

Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were considered in determining the quality of the identified evidence, including study design and methodology, risk of bias and applicability of the evidence.

Criterion 4: There should be a simple, safe, precise and validated screening test.

Criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Key Question: What is the reported performance of screening strategies for detecting thrombophilia in neonates and adults?

The UK NSC review protocol states that of interest in this question is the accuracy of tests, age of screening and the timing and repetition of testing (in adults) and that studies of consecutively enrolled populations with no prior risk should be prioritised. The review protocol also noted two categories of studies that might be described but would not provide direct evidence to answer the question. These were studies seeking to explore a reference range for testing in the neonatal population and development of proof of concept studies[1].

Description of the evidence

Adults

In the current review, of the 20 studies identified as potentially relevant during title and abstract sifting, 11 related to this criterion for adults. After review of the full texts, no studies met the criteria for inclusion. Reasons for excluding studies at this stage included:

- a study focusing on the prevalence of mutations associated with thrombophilia rather than the performance of a screening test
- a study evaluating the performance of a activated protein resistance screening test in a population of hospital patients referred for testing from a range departments including inpatients, obstetrics and gynaecology and oncology
- 2 studies of screening patients with DVT for thrombophilia to define risk factors for DVT
- guidelines considering testing adults with idiopathic VTE and their asymptomatic family members
- a case-control study of coagulation tests as a first-line test for prothrombin G-20210-A polymorphism
- a case-control study testing for activated protein C resistance

[†]These criteria are available online at UK NSC evidence review criteria (January 2016)

- a study calculating likelihood ratios for multiple genetic tests associated with venous thrombosis from simulated case-control data
- 2 descriptive reviews
- a discussion paper.

Neonates

In the current review, of the 20 studies identified as potentially relevant during title and abstract sifting, 7 related to this criterion for neonates. After review of the full texts, no studies were included. Reasons for excluding studies at this stage included:

- studies that were about screening neonates for other disorders eg metabolic disorders (not about screening for thrombophilia)
- a study about the interpretation of coagulation tests in neonates
- a study exploring the prevalence of factor V Leiden mutation in a population of neonates
- a study about the early development of a test.

Discussion

After review of the full papers no studies met the criteria for inclusion as no studies explored test performance or screening strategies in consecutively enrolled populations of adults or neonates. When studies were about thrombophilia testing the study populations were people who had already had a thrombotic event or their family members or patients referred for testing. Other studies explored the prevalence of mutations associated with thrombophilia rather than test performance.

Summary: Criteria 4 and 11 not met

No studies on screening strategies for detecting thrombophilia in neonates or adults were identified. These criteria are therefore not met.

Criterion 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

Key Question: What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

The UK NSC review protocol states that of interest in this question are different treatments, dose and duration of treatment and harms/ adverse effects[1].

Description of the evidence

Adults

In the current review, of the 20 studies identified as potentially relevant during title and abstract sifting, 1 related to this criterion for adults. After review of the full text, this study was not

included. The study was excluded at this stage because the population was patients screened for thrombophilia after a thrombotic event and who therefore did not have screen-detected thrombophilia.

Neonates

In the current review, of the 20 studies identified as potentially relevant during title and abstract sifting, 1 related to this criterion for neonates. After review of the full text, this study was not included. The study was excluded at this stage because the study population were being treated for a metabolic disorder rather than for thrombophilia.

Discussion

After review of the full papers no studies met the criteria for inclusion.

Summary: Criterion 9 not met

No studies were identified that assessed the effectiveness of thromboprophylaxis in screen-detected adults or neonates. This criterion is therefore not met.

Conclusions and implications for policy

This report assesses screening for thrombophilia in adults and newborns against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

Recommendation

The review concluded that the evidence base is insufficient to evaluate screening for thrombophilia in adults or neonates. The lack of studies meeting the inclusion criteria suggests that there would be limited value in routinely updating this review.

Limitations

This review identified no studies addressing the key questions of interest.

Search strategy

A scoping literature search on screening for thrombophilia in adults and newborns was performed by the UK NSC in August 2016.

SOURCES SEARCHED: Medline (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, OVID MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present)

DATES OF SEARCH: 19th August 2016

ADULT SEARCH STRATEGY

1. exp Thrombophilia/ **(23295)**
2. thrombophilia$.tw. **(5021)**
3. (Factor V Leiden or factor V or FVL).tw. **(7045)**
4. ((prothromb$ or antithromb$ or thrombophilia$ or protein C or protein S) adj2 (deficienc$ or abnormalit$ or defect$)).tw. **(4219)**
5. (methylenetetrahydrofolate reductase or MTHFR).tw. **(6364)**
6. hypercoagulable.tw. **(3801)**
7. factor VIIIc.tw. **(627)**
8. hyperhomocysteinaemia.tw. **(770)**
9. fibrinogen.tw. **(41347)**
10. acquired APC resistance.tw. **(44)**
11. Antiphospholipid Syndrome/ **(7042)**
12. antiphospholipid syndrome.tw. **(6305)**
13. APS.tw. **(9266)**
14. Hughes syndrome.tw. **(139)**
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 **(93266)**
16. Mass Screening/ **(89662)**
17. (screen$3 or test or tests or testing or detect$3).ti. **(694002)**
18. 16 or 17 **(730339)**
19. ((healthy or adult or general) adj population).tw. **(95285)**
20. 15 and 18 and 19 **(44)**
21. adult*.ti,ab. **(977074)**
22. 15 and 18 and 21 **(94)**
23. 20 or 22 **(133)**

NEWBORN SEARCH STRATEGY

1. exp Thrombophilia/ **(23295)**
2. thrombophilia$.tw. **(5021)**
3. (Factor V Leiden or factor V or FVL).tw. **(7045)**
4. ((prothromb$ or antithromb$ or thrombophilia$ or protein C or protein S) adj2 (deficienc$ or abnormalit$ or defect$)).tw. **(4219)**
5. (methylenetetrahydrofolate reductase or MTHFR).tw. **(6364)**
6. hypercoagulable.tw. **(3801)**
7. factor VIIIc.tw. **(627)**
8. hyperhomocysteinaemia.tw. **(770)**
9. fibrinogen.tw. **(41347)**
10. acquired APC resistance.tw. **(44)**
11. Antiphospholipid Syndrome/ **(7042)**
12. antiphospholipid syndrome.tw. **(6305)**
13. APS.tw. **(9266)**
14. Hughes syndrome.tw. **(139)**
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 **(93266)**
16. Mass Screening/ **(89662)**
17. (screen$3 or test or tests or testing or detect$3).ti. **(694002)**
18. Neonatal Screening/ **(8313)**
19. 16 or 17 or 18 **(733697)**
20. Infant, Newborn/ **(543365)**
21. (newborn$ or neonatal$ or infant$).tw. **(547848)**
22. 20 or 21 **(845359)**
23. 15 and 19 and 22 **(83)**

GENERAL SEARCH STRATEGY

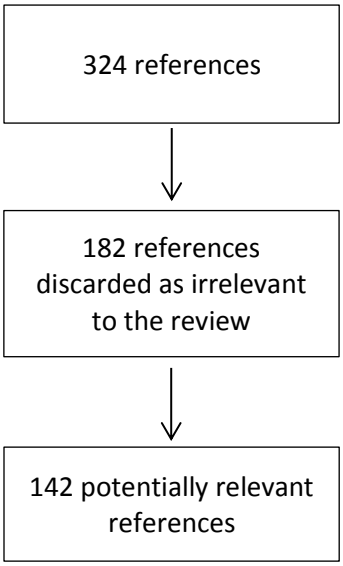
1. thrombophilia$.ti. **(1949)**
2. screen$3.ti. **(139942)**
3. 1 and 2 **(108)**

Table 2: Results of the literature search

Search	Number of results
Adult screening	133
Newborn screening	83
General search	108
Total	**324**

Duplicates and non-English references were removed and 324 were briefly sifted by title to remove obviously irrelevant references. 77 adult references, 56 newborn references and 9 general references were considered potentially relevant and were passed to the SPH reviewer for further consideration.

Figure 1: Flow diagram summarising the results of the reference sifting process



Key question PICOS[‡]

Question	What is the reported performance of screening strategies for detecting thrombophilia in neonates and adults?
Notes	The data should be reported separately for neonates and adults. The question should look at: • tests • age of screening • timing and repetition (in adult) Studies of consecutively enrolled populations with no risk should be prioritised. Studies seeking to explore a reference range for testing in the neonatal population might be described but would not provide direct evidence to answer the question. Studies of screening for individual thrombophilias or panels of thrombophilias should be included. Developmental or proof of concept studies (eg two gate study designs, studies considering a reference range to inform screening in the general neonatal population etc) might be described but should not be considered direct evidence to answer the question.
Population	• Neonates (excluding neonates with pupura fulminans) • Adults (excluding a risk group such as people taking the oral contraceptive pill, hormone replacement therapy, patients following major orthopaedic surgery and pregnant women)

Intervention	Tests for thrombophilia such as:
	• Antithrombin deficiency
	• Protein C deficiencies
	• Free protein S deficiencies
	• Factor V Leiden mutation
	• Prothrombin gene mutation (G-20210-A)
	• Activated protein C (APC) Resistance Assay
	• Methylenetetrahydrofolate reductase (MTHFR) mutation
	• Antiphospholipid antibodies (aPL)
	  • Anticardiolipin antibodies (aCL)
	  • Lupus anticoagulant (LA)
	  • Anti-beta2-glycoprotein (anti-B2GP1)

Comparator	Open
Outcomes	Study reporting clinical performance measures, and SRs of these: • Sensitivity • Specificity • False positive rate • False negative rate • PPV/ NPV

[‡] Population, Intervention, Comparator, Outcomes

Question	What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?
Note	The data should be reported separately for neonates and adults. This question should look at: • different treatments • dose and duration of treatment • harms/ adverse effects
Population	• Neonates (excluding neonates with pupura fulminans) • Adults (excluding a risk group such as people taking the oral contraceptive pill, hormone replacement therapy, patients following major orthopaedic surgery and pregnant women)
Intervention	Anticoagulation management comprises any prescription of anticoagulants.
Comparator	Neonates or adult with thrombosis who are not screened and subjected to anticoagulation management. N/a is the study is observational
Outcomes	• Thromboembolic events (including fatal events) – venous events for population with venous thrombosis including DVT, pulmonary embolism, venous stroke, arterial events for population with arterial thrombosis including arterial stroke and myocardial infarction • Mortality • Adverse effects of anticoagulation treatment (eg haemorrhage) • Anticoagulation management measures, including whether or not an anticoagulant is prescribed, frequency of International Normalised Ratio (INR) testing, INR target, duration of anticoagulant prescription, duration of follow-up patient.

References

[1] UK NSC. Neonatal and general adult populations screening for thrombophilia. Briefing Note. October 2016

[2] Yapijakis C. Antoniadi T. Salavoura K. Voumvourakis C. Vairaktaris E. Potential prevention of thromboembolism by genetic counselling and testing for two common thrombophilia mutations. In Vivo 2012, 26: 165-172

[3] National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Clinical Guideline 144. Published June 2012

[4] UK NSC. Evaluation of antenatal screening for thrombophilia against National Screening Committee handbook criteria, with consideration of neonatal screening and general population screening. 2010