Evaluation of Antenatal Screening for Thrombophilia against National Screening Committee Handbook Criteria, with consideration of neonatal screening and general population screening

Background – the current strategy for detecting thrombophilias antenatally in the UK

Currently in the UK testing for thrombophilias is offered during early pregnancy on the basis of clinical risk factors. These include previous fetal loss, still birth, history of pre-eclampsia and severe intrauterine growth retardation. The criteria for selective screening are widely debated and varies between different maternity units.

The current testing strategies that are implemented in the UK have been shown to have variable implementation in different geographical areas, and in addition the range of thrombophilias tested for is inconsistent [1].

Articles which look at inclusion criteria for testing currently in use in the UK, such as offering a test to women who have had a prior adverse pregnancy outcome, find that even these criteria are not evidence-based[1]. For example, some studies demonstrate no association between maternal thrombophilias and early pregnancy loss [2] and there is controversy over screening women with gestational complications other that venous thromboembolism (VTE) and late pregnancy loss[3,4]. Other criteria for testing are also debated, for example some suggest benefit from offering testing to women who have first degree relatives with thrombophilias [5], whilst others state that inherited thrombophilia testing is not indicated [6].

Further studies describe how the results of thrombophilia screening do not influence clinical management in the majority of cases [7]. Other research describes an 'overutilisation' of thrombophilia screening, suggesting that thrombophilia panels should be reserved for special circumstances for which there would be a specific clinical impact [8]. In 2006 the biggest study in this field, the TREATS systematic review and cost-effectiveness analysis[9], undertaken as an HTA report, recommended that universal thrombophilia screening in women during pregnancy is not supported by the evidence.

In summary, selective testing rather than universal screening is recommended by much of the literature [9,10,11,12,13]. Even selective testing is implemented variably and its value debated by some parties.

The Condition
1. The condition should be an important health problem

Heritable thrombophilia is a broad term used to describe a number of genetic variants which cause an increased risk of VTE by increasing blood coagulability. During pregnancy and immediately following delivery, there are physiological changes to natural procoagulants, anticoagulants and fibrinolytic activity such that the risk of thrombosis increases [14].

In the general population the most important clinical outcome which may result from thrombophilia is venous thromboembolism (VTE), which may present as deep vein thrombosis (DVT) or pulmonary embolism (PE).

In pregnancy, thrombophilia results in significantly increased risk of adverse outcomes including severe pre-eclampsia (OR 1.37 – 3.49), early pregnancy loss (OR 1.4 – 6.25), late pregnancy loss (OR 1.31 – 20.09), placental abruption (OR 1.42 – 7.71) and intrauterine growth retardation (OR 1.24 – 2.92) [10.15]. These complications are prevalent in approximately 8% of the general population[10,16].

2. i) The epidemiology of the condition should be known
ii) The natural history of the condition should be understood
iii) There should be a recognized latent period or early symptomatic stage

Thrombophilia is inherited (including mutations of the genes which encode antithrombin, protein C, protein S, fibrinogen, prothrombin and factor V Leiden) or acquired (antiphospholipid syndromes leading to lupus inhibitor activity and/or elevated cardiolipin levels). In addition thrombophilia may result from the combination of genetic and environmental factors (elevated factor VIII, activated protein C resistance not due to factor V Leiden, or elevated homocysteine levels for example).

Considering these different aetiologies, enhanced coagulability has been shown have relatively high prevalence[17,18] of more than one in 20 of the general population. For example, factor V Leiden alone has a prevalence of 4% and prothrombin gene mutation has a prevalence of 1%.

The clinical outcomes vary according to the underlying thrombophilia, but can result in VTE, DVT, PE and pregnancy complications as described above. Certain genetic mutations have higher risks of adverse outcomes (such as VTE) than others.

The risk of VTE is higher in women with other risk factors including pregnancy, surgery, the combined oral contraceptive pill and hormone replacement therapy. In addition, there are differences in the prevalence of thrombophilias in different ethnic populations[19].

Thrombophilias are asymptomatic until complications such as VTE or PE occur – there is no early symptomatic stage, nor recognised latent period.

3. All cost-effective primary prevention interventions should have been implemented as far as practicable

There are no primary prevention interventions for the inherited and acquired forms of thrombophilia. Secondary prevention for pregnant women for whom a thrombophilia is detected takes the form of heparin and/ or aspirin. Some UK guidelines suggest post-partum thromboprophylaxis for previously asymptomatic carriers of Factor V Leiden although this is controversial. All of those diagnosed would also be given patient information giving advice on risk factors.

The Test

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

There is a typical range of screening tests for thrombophilias which usually includes testing for lupus anticoagulant, prothrombin gene mutation, antithrombin III, protein C, protein S, Factor V Leiden and factor VIII assays. This test requires 30mls of blood. However recent research suggests that across the UK labs in different geographical areas are inconsistent in the range of thrombophilias for which they test, with testing for proteins C and S deficiency and factor V Leiden being the most commonly employed[1].

5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Some of the tests are positive/ negative, whilst others are 'normal' or 'low' with agreed cut-offs. Reference ranges are available for adults, although possibly not newborn babies for all conditions.

6. The tests should be acceptable to the population

The blood test itself is a relatively quick and side-effect free procedure. However there are no studies which address its acceptability as a test offered to an unselected population.

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals

Once a positive result for specific thrombophilias are obtained, there would be no further diagnostic investigations of these individuals, and in the majority of cases there would be no interventions, thus no choices available, unless they had

another risk factor for VTE according to the selective screening protocols already in place (see below).

However, for some conditions the new diagnosis may lead to first degree relatives being aware of an increased likelihood of them also having the condition. This may require consideration of the need for a cascade testing strategy as a consequence of a universal screening programme. The details of this are beyond the remit of this evaluation.

The Treatment

8. There should be an effective treatment or intervention for patients identified through early detection

Existing research does not suggest that the identification of heritable thrombophilia can usefully influence management[20]. For pregnant women interventions would only be offered if they had another risk factor in addition to a positive blood test result, in accordance with the current practice. The only exceptions to this would be the very rare instance in which blood tests reveal more than one mutation, a homozygous result or for specific types of AT3 deficiency. The intervention in such cases would usually be increased clinical supervision antenatally and post-partum heparin. Long-term anticoagulant therapy would not usually be indicated. In addition women would be counseled and provided with patient information on the avoidance of general risk factors for VTE (for example stop smoking).

9. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

A universal screening programme for pregnant women would have no criteria other than pregnancy. Once women with specific thrombophilias were identified, then they would be treated according to local guidelines.

10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.

Generally, testing for hereditary thrombophilia does not alter the clinical management of patients [21]. However, in the UK there are currently standard management guidelines for women with risk factors for VTE, which in some cases include post-partum heparin and in some cases other treatments.

The Screening Programme

Studies of thrombophilia screening predominantly focus on specific gene mutations, rather than thrombophilia in general, or address selective testing rather than universal screening programmes.

11. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

The literature studies revealed no randomised controlled trials of universal antenatal screening programmes for thrombophilias. It is likely that such studies would not be funded or granted ethical approval due to the consensus that such a screening programme is not cost-effective nor appropriate.

However a recent HTA systematic review and cost-effectiveness analysis of thrombophilia in high-risk situation (the TREATS study) included studies of thrombophilia testing in pregnancy. However, the majority of studies included in this work were retrospective case control studies and none were studies of screening programmes, due to the dearth of research in this area. Only two of the included studies were randomised, one of which was an RCT – both of these studies were of women with additional risk factors. Despite these limitations, the TREATS study was able to explore the cost-effectiveness of screening programmes as discussed in more detail below (section 14), demonstrating that universal screening in pregnancy prevented 59 out of 2921 complications arising per 10,000 women screened, and found this to be less cost-effective than a more selective approach. [9]

Even when studies consider pregnant women known to have acquired or inherited thrombophilias, there is no good research evidence of the effects (positive or negative) of heparin on pregnancy outcomes[22]. Potential negative effects would be likely to include bleeding. Further studies in this area are expected soon (deVries 'FRUIT' study and Rodgers 'TIPPS' study).

Furthermore, even studies of selective approaches to testing for thrombophilias demonstrate controversy over benefits in terms of reductions in mortality and morbidity, as described in the background section of this evaluation.

12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Health Professionals
No formal research studies of health professionals were revealed by the literature search. However in the UK and overseas the current consensus appears to be that universal screening of pregnant women for thrombophilias should not be introduced [20].

The Public
No formal research studies of public views on screening pregnant women for thrombophilias were revealed by the literature search. Were such a screening programme to be strongly considered, such consultation with the public would be essential.

13. The benefit from the screening programme should outweigh physical and psychological harm (caused by the test, diagnostic procedures and treatment).

i) Benefits
Potentially the benefit would be to prevent VTE and adverse pregnancy outcomes as described above. However because of the absence of randomised controlled trial evidence for universal screening programmes in this area, the true benefit of the screening programme can only be hypothesized. Nevertheless, the TREATS evaluation analysed studies of the effectiveness of prophylactic interventions in thrombophilia, in women who would theoretically be those identified through a universal screening programme. These studies found some benefit from aspirin and heparin in preventing pregnancy loss and minor bleeding, but these associations were not statistically significant. [9]

ii) Harms
There are a number of potential adverse outcomes including anxiety for those considering screening, awaiting test results or receiving positive results. Unnecessary testing may overestimate risks, for example even for those with a screen positive result, VTE is not certain since some studies demonstrate 40% of women tested positive never develop VTE. Conversely, a negative result may provide false reassurance. Those who screen positive may be prescribed potentially unnecessary and hazardous treatments, including anticoagulants, with their resultant side-effects, complications and drug interactions. A futher potential harm from screening is that some insurance companies may increase premiums for those with screen positive results, even if they experience no resultant health problems. [20,23]

14. The opportunity cost of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole.

i) Cost-effectiveness studies

Clearly arguments based on cost-effectiveness are based on the values one places on avoiding adverse events [24], and must be balanced with consideration to opportunity costs.

The TREATS report addressed cost-effectiveness of screening for thrombophilias in high risk situations including pregnancy [9]. The other high-risk situations studied in this work were use of combined oral oestrogens, hormone replacement therapy and orthopaedic surgery.

This work demonstrated that universal screening in pregnancy would be the most expensive strategy (of those studied) to implement, costing £5,374,890 to screen a cohort of 10,000 women. In addition, although the HTA analysis found that for all high risk situations, selective screening prevented fewer cases of adverse clinical complications that universal screening (7 versus 59 cases for pregnancy screening), selective strategies had slightly lower incremental cost-effectiveness ratios (ICERs) than universal screening, indicating increased cost-effectiveness. However for pregnancy, the difference between ICERs for selective and universal screening was very small (£81,250 versus £81,554 respectively). Yet, it is relevant that these cost-effectiveness calculations only measured direct health service costs and are therefore likely to underestimate the true costs of implementing the screening programmes. When compared with selective testing, universal screening of a theoretical population would only prevent an additional 1.78% (52 of 2921 complications in total) of all clinical complications.

The report recommended that universal thrombophilia screening in women is not supported by the evidence for any of the four high risk situations studied, including pregnancy, and that selective screening based on prior venous thromboembolism history is more cost-effective than universal screening[9]. In addition to these cost-effectiveness arguments, this recommendation is strengthened by other factors including the lack of evidence to establish the value of universal screening. Potential harms of universal screening, including psychological distress and over-use of unnecessary and harmful treatments, are discussed later.

Other reviews of the literature concur that universal screening for thrombophilia in pregnancy is unjustified due to the poor cost-benefit ratio[25].

ii) Direct and indirect costs

The direct healthcare costs calculated as part of the TREATS study above consisted of the diagnostic tests, staff time and cost of prophylaxis. In addition their calculations included the costs of adverse complications (diagnostic tests, admissions, outpatient appointments, counseling and drug treatments). It is unclear to what extent the calculations included counseling prior to screening.

However there are other factors beyond these costs:-

- Patients' personal travel expenses to and from appointments for screening and resultant treatment, although direct costs, do not appear to have been included in the TREATS analysis;

- Patients' loss of income from time off work to attend appointments for screening and resultant treatment;
- Stress and anxiety experienced by patients or their families.
- A positive test result may also lead to consideration of screening the patient's relatives, with its own direct and indirect costs.

15. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

Should a universal screening programme for pregnant women be introduced, clear quality assurance standards would need to be put into place. No such standards already exist.

16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

Introduction of universal screening during pregnancy would have resource implications in addition to the financial cost of implementing the programme. In more detail, the impact would be felt in the following ways:-

- There would be considerably increased workload for haematologists and laboratory staff in the context of already understaffed professions in the UK;
- Facilities for processing blood specimens are not available in every hospital and it is likely these would have to be sent to selected laboratories in each region;
- Counseling and informed consent of all pregnant women prior to the test would have a significant impact on midwifery resource. Staff would require specific and quality-assured training in counseling for thrombophilia screening, with regular updates. In addition training of staff in counseling when giving results would be needed.
- Laboratory testing of all pregnant women would have a considerable impact on laboratory staff time;
- Negative and positive results will require feedback of results to the women which would again impact on midwifery resources;
- Positive results will also require the patients' referral to a haematologist, which would impact upon haematology department resources;
- Patients with positive results may require additional antenatal care with greater supervision and a requirement for delivery to take place in a medically-managed obstetric unit rather than a home birth or midwifery-led unit. This would have implications for obstetric department resources and the medicalisation of childbirth;
- Patients with positive results may require long-term follow-up with either the haematologist or GP, with the associated impact upon haematology department and primary care resources;

- Some patients will require long-term anticoagulant therapy, with its associated impact upon anticoagulant clinic resources (currently pharmacist-led anticoagulant clinics cost around £125 per case per year.

The absolute impact upon resources will depend upon the number of women who take up screening, and of these the proportion who have positive results. If, hypothetically, 90% take up screening, and of these 1 in 20 have a positive result for one of the ten conditions tested for, this would lead to a referral of 4.5% of pregnant women to haematology departments.

17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services)

Other alternatives to universal screening of pregnant women include:

- No screening.
- Selective screening according to know risk factors, including personal history of VTE, first-degree relative with thrombophilia, previous adverse pregnancy outcome (recurrent miscarriage, late fetal loss, preeclampsia, placental abruption and intrauterine growth retardation). This is the currently adopted option in the UK, although even screening women with certain risk factors (e.g. previous adverse pregnancy outcome) remains controversial because interventions are unproven at present and testing is undertaken inconsistently in different units[1].

Neonatal screening for thrombophilias

Many studies of childhood thrombophilias indicate that paediatric thromboembolism, even in the presence of an inherited thrombophilia, is a multifactorial disorder [26,27].

Testing for thrombophilias, even in symptomatic neonates, is controversial [28]. For example, thrombophilia testing is recommended by some for children who experience perinatal thrombosis, rather than universal screening of all neonates[29]. In addition, as discussed earlier, some authors suggest that first-degree relatives of those with symptomatic inherited thrombophilias should be screened antenatally or around the time of puberty[11] if there are concerns about pregnancy complications, but there is no evidence for screening neonates even in this highly selected subgroup.

If considering universal neonatal screening, age-specific reference ranges would need to be used to interpret the results of thrombophilia testing in neonates and may not currently exist for all thrombophilias currently tested for in adults.

There would be a similar and considerable impact on the NHS as discussed previously for antenatal screening, including the costs of the battery of tests,

midwife time, laboratory staff time and the impact of following up babies in haematology departments. In addition for neonates there would be an impact upon paediatric departments and health visiting services.

When the issues above are considered alongside the view widely held among professional groups that routine testing for hereditary thrombophilias, even in symptomatic patients does not generally alter the management of patients, the argument for neonatal universal screening is further weakened.

This review does not recommend universal thrombophilia screening for pregnant women, who are inherently at higher risk of thrombo-embolic events than the general population due to the changes to coagulation during pregnancy. There is awareness that generally neonates are at much lower risk of thrombosis than pregnant women, and there is no need to consider pregnancy complications of thrombophilias as was required in the review of antenatal screening above. With consideration to this and to the issues highlighted above, it is therefore not appropriate to recommend further reviews of thrombophilias screening in wider population groups at even lower risk, for example neonates. Relevant professional groups may wish to consider this area in more detail.

Universal screening for thrombophilias in the general population

As for neonatal screening described above, the general population are at lower risk of thrombo-embolic events than pregnant women, therefore risks of screening even further outweigh potential benefits. This document did not set out to review other high risk situations, Nevertheless, the TREATS study[9], in addition to addressing antenatal screening for thrombophilias, looked at other potentially high-risk situations including people taking the oral contraceptive pill, hormone replacement therapy and following major orthopaedic surgery. As for antenatal screening, the study did not recommend universal screening for people with these risk factors. When the TREATS recommendation is considered in the context of the potential benefits and harms of a universal screening programme as already described in the report then the case for universal screening of the general population, is further weakened as such a programme would not meet National Screening Committee criteria. However selective testing of high risk groups may be appropriate and should be reviewed by the relevant bodies.

Summary and recommendations

In 2000 a workshop was held to address the need for screening for heritable thrombophilias and key stakeholders recommended that this would be inappropriate[30].

Since this time, the biggest study in this field, the TREATS systematic review and cost-effectiveness analysis, undertaken as an HTA report [9], recommended that universal thrombophilia screening in women during pregnancy is not supported by the evidence. Since this work no further high quality research evidence has

been published which suggests otherwise, and many studies reflect the TREATS review in stating that universal screening is not appropriate and indeed even some selective testing strategies are not beneficial or evidence-based. In addition, the absence of randomised controlled trial research addressing universal antenatal thrombophilia screening seriously weakens proposals for such a programme. Therefore antenatal screening for thrombophilias does not meet National Screening Committee criteria and would not be supported by this review.

Screening other groups such as neonates, the general population and individuals with risk factors such as being on the oral contraceptive pill, hormone replacement therapy or following major orthopaedic surgery was not the original purpose of this review. However the evidence demonstrates that universal screening of the general population or neonates is not supported and would not meet National Screening Committee criteria.

In not recommending screening for thrombophilias as a group of conditions, this report is therefore not recommending screening for any of the individual conditions which make up this group, for example factor V Leiden.

In conclusion this review does not recommend universal thrombophilias screening for pregnant women. The National Screening Committee does not cover more selective approaches to testing within its remit.

Recommended further work for potentially high-risk populations

Thrombophilia testing may be appropriate for selected high-risk populations, as currently operates in the UK. However such a selective screening programme should be reviewed by relevant professional groups in the context of existing controversy and debate in this area. This review recommends that the British Society for Haematology, the Royal College of Obstetricians and Gynaecologists, the Royal College of Pathologists and the National Institute for Health and Clinical Excellence should liaise to produce evidence-based definitive guidance on testing in different patient groups, including relatives of those with inherited thrombophilia. This is the only way that the current controversy and variation in approach can be addressed in this area.

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