Antenatal screening for thrombophilia

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

Version: Final

Bazian Ltd.

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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://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations List

APC	activated protein C
aCL	anticardiolipin antibodies
anti-β2GPI	anti-β2 glycoprotein I antibodies
aPLs	antiphospholipid antibodies
APS	antiphospholipid syndrome
AT	antithrombin
CI	confidence interval
FRUIT	FRactionated heparin in pregnant women with history of Uteroplacental Insufficiency and Thrombophilia
FVL	factor V Leiden
IU	international units
IUGR	intrauterine growth restriction
LA	lupus anticoagulant
LMWH	low molecular weight heparin
MA	meta-analysis
MTHFR	methylene tetrahydrofolate reductase
NW	network
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
PT	prothrombin
PW	pairwise
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RD	risk difference
RPL	recurrent pregnancy loss
RR	relative risk
SGA	small for gestational age
SR	systematic review
TIPPS	Thrombophilia in Pregnancy Prophylaxis Study
TREATS	Thrombosis: Risk and Economic Assessment of Thrombophilia Screening
UFH	unfractionated heparin
VTE	venous thromboembolism

Plain English Summary

This review aimed to see whether all women should be offered screening for thrombophilia during pregnancy.

Thrombophilia is a broad term that covers a number of conditions where the blood clots easily. The condition may be hereditary or it may have developed (acquired). During pregnancy, women with thrombophilia may be at increased risk of blood clots in the leg veins (deep vein thrombosis), or other complications such as high blood pressure, or birth of a preterm or small baby.

Currently universal thrombophilia screening for all pregnant women is not performed. Thrombophilia testing is carried out on a selective basis if the woman has risk factors.

The last UK NSC review carried out in 2010 concluded that universal antenatal screening should not be performed. No studies had assessed universal screening of all women, and no studies could inform whether anti-clotting treatment was safe and effective at preventing adverse pregnancy outcomes in screen-detected women. There was also uncertainty whether all types of thrombophilia carried risk of pregnancy complications.

The current review aimed to see whether evidence published over the past six years suggests that the decision not to perform universal thrombophilia screening for all pregnant women should be reconsidered.

The review found that the evidence needed to inform the effectiveness of a universal thrombophilia screening programme has not been published.

No studies have examined universal thrombophilia screening for all pregnant women, either compared with no screening, or with the current practice of selective testing of women with risk factors. Also no studies have examined the effectiveness and safety of providing anti-clotting treatment to screen-detected women. Two recent large trials have assessed the use of low molecular weight heparin (LMWH) in pregnant women with thrombophilia, but these women all had additional risk factors, such as prior pre-eclampsia or small baby, so do not represent all women who would be detected through a universal screening programme.

High quality research is needed in several areas in order to better assess whether there is value in carrying out universal thrombophilia screening of all pregnant women. Studies need to compare universal screening of all women with the current practice of testing based on risk factors and see whether this affects pregnancy outcomes. Studies would then need to see whether giving anti-clotting treatment to all screen-detected women is safe and reduces risk of pregnancy complications.

A review would also be valuable that gathers together the large number of studies published to date that have looked at the link between individual thrombophilia types and individual pregnancy outcomes. This would better establish the risks associated with each of the hereditary and acquired thrombophilias and guide treatment needs.

Executive Summary

Purpose of the review

This rapid evidence review considers whether the volume, quality and direction of evidence published between January 2010 and June 2016 indicates that the current recommendation not to perform universal thrombophilia screening for all pregnant women should be changed.

Background

Thrombophilia is a broad term that describes a number of variants that, during pregnancy and in the immediate postnatal period, carry an increased risk of venous thromboembolism (VTE) and adverse pregnancy outcomes due to increased blood coagulability. Thrombophilia can be either hereditary (factor V Leiden, prothrombin or MTHFR mutation, antithrombin, protein S or protein C deficiencies) or acquired (e.g. antiphospholipid antibodies/syndrome, APC resistance, hyperhomocysteinaemia).

There are a range of diagnostic assays available to test for the different thrombophilias, and there may be inconsistency across UK labs in the variants tested for.

Current antenatal care in the UK performs selective testing for hereditary thrombophilia in women who have a first-degree relative with an unprovoked or oestrogen-associated VTE before the age of 50, or women with prior second trimester loss. Women with past VTE themselves, or other risk factors in the current pregnancy (e.g. pre-eclampsia), wouldn't normally need thrombophilia testing as they'd be considered candidates for thromboprophylaxis anyway.

Thromboprophylaxis – usually with low molecular weight heparin (LMWH) – may be considered for women identified to have thrombophilia, but this will likely depend on the identified variant as they are associated with different risk. Women with antithrombin, protein C or S deficiencies, homozygotes or compound heterozygotes are thought to be at highest risk and would normally be prescribed thromboprophylaxis, even if they have no other risk factors. Those heterozygous for other variants or with antiphospholipid antibodies are normally only treated if they have additional risk factors.

Previous/ Current UK NSC Review

The most recent UK NSC external review conducted in 2010 concluded that universal antenatal screening for thrombophilia was not recommended.

This conclusion was primarily based on the largest study in this field, the TREATS[1] health technology appraisal. TREATS[1] concluded that overall thrombophilia increases risk of VTE and adverse pregnancy outcomes, but the risk differs according to the underlying variant. The largest body of evidence related to factor V Leiden and prothrombin mutation, with fewer studies available to inform the risk associated with rarer hereditary or acquired thrombophilias.

TREATS[1] found no studies that had compared universal antenatal screening of all pregnant women either with no screening or with other screening programmes. There was also

insufficient evidence that antenatal thromboprophylaxis is safe and effective in reducing risk of pregnancy complications.

The current review aimed to examine these gaps in the evidence and address three key questions:

- Whether there is evidence that the different hereditary or acquired thrombophilia variants are associated with risk of adverse pregnancy outcomes
- Assessing the performance of universal thrombophilia screening strategies for all pregnant women
- Whether there is evidence that treating screen-detected women is safe and effective in reducing risk of adverse pregnancy outcomes.

Findings and gaps in the evidence

The review found that:

- No studies have assessed strategies of universal thrombophilia screening for all pregnant women, either compared with no screening or with current practice of selective testing based on risk factors. Neither were there any studies available to inform on the performance of universal screening tests, cut-offs to use or timing of screening during pregnancy. Therefore there is no evidence to suggest that universal screening of all pregnant women would offer any benefit compared with current practice.
- No comparative studies have assessed thromboprophylaxis in screen-detected women, or in women without additional risk factors who would be representative of all screen-detected women. Two RCTs have assessed the effectiveness of thromboprophylaxis in women with hereditary thrombophilia or antiphospholipid antibodies, but these trials only included women with additional pregnancy risk factors, such as prior pregnancy loss, pre-eclampsia or SGA baby. Many of these women would meet current treatment criteria and do not represent the full screen-detected population. Even in high risk women these trials also gave inconclusive findings on the safety and effectiveness of treatment.
- Since the 2006 TREATS[1] review, a large volume of cohorts and case controls have been published that have assessed the link between individual thrombophilia variants and individual pregnancy outcomes. To better assess natural history and confirm the adverse pregnancy outcomes associated with each variant would require pooling of all of these studies with an updated meta-analysis for each. Given that the findings on screening and treatment seemed to preclude universal screening at the current time, the decision was made on discussion with UK NSC not to proceed with this analysis within the context of this evidence review.

Recommendations on screening that can be made on the basis of the current review

The findings of the current review do not indicate that the current recommendation not to perform universal antenatal screening for thrombophilia should be reconsidered. There was an absence of evidence required to answer the key questions set by this review.

Further high quality prospective studies would be needed:

- To assess whether universal thrombophilia screening of all pregnant women improves pregnancy outcomes compared with no screening or with current practice of selective testing based on risk factors

- That examine the accuracy of different panels of screen tests, and the optimal timing of screening during pregnancy
- That examine the effectiveness and safety of thromboprophylaxis in women with thrombophilia who are not selected on the basis of additional risk factors and so would be representative of all screen-detected women

As above, an updated systematic review with meta-analysis would be valuable to pool the epidemiological evidence published to date and better establish the risk associated with each of the individual hereditary and acquired thrombophilia variants. This could help guide treatment need.

Limitations: This was a rapid review conducted over an 8 week period. It is not a comprehensive review of all literature on thrombophilia in pregnancy, addressing focused key questions and reviewing only literature published over the past six years. Searching was limited to three literature databases. We excluded studies available in non-English language or at abstract level only, and did not review grey literature. Selection and appraisal of studies was predominantly undertaken by one reviewer, with any queries resolved through discussion with a second reviewer and with the UK NSC.

Introduction

Thrombophilia

Thrombophilia is a broad term used to describe an increased tendency for the blood to clot. During pregnancy, which is itself a hypercoagulable state, there is an increased risk of venous thromboembolism (VTE) and other adverse pregnancy outcomes.

Thrombophilia can be either hereditary (e.g. factor V Leiden, prothrombin mutation) or acquired (e.g. antiphospholipid syndrome). Between a quarter and a half of women with pregnancy-related VTE are found to have hereditary thrombophilia.[2]

Universal antenatal screening for thrombophilia is not currently recommended. In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend that pregnant women are assessed for VTE risk factors such as previous VTE, increased age, obesity, smoking, and obstetric risk factors such as preterm birth or pre-eclampsia.

The RCOG also advises that pregnant women without these risk factors are considered for hereditary thrombophilia testing if they have a first-degree relative who has had an unprovoked or oestrogen-associated VTE before the age of 50 years,[2] or if they have had a prior second-trimester pregnancy loss.[3] It is advised that tests include factor V Leiden, prothrombin mutation and protein S deficiency.

Women who've had a past unprovoked or oestrogen-associated VTE themselves don't need hereditary thrombophilia testing as they'd normally be considered for thromboprophylaxis as part of routine care.[2, 4] However, RCOG advise that these women are tested for antiphospholid antibodies, or for antithrombin deficiency if they also have a family history of VTE, as these conditions may alter prophylaxis indications, as below.[2]

The need for thromboprophylaxis depends on the identified variants as these carry different risk. Women with antithrombin, protein C or S deficiency, and those with more than one variant (including homozygous factor V Leiden or prothrombin gene mutation and compound heterozygotes), are advised thromboprophylaxis (usually with low molecular weight heparin [LMWH]) during pregnancy and for six weeks postpartum.[2]

Women who are heterozygous for factor V Leiden or prothrombin gene mutation, or who have antiphospholipid antibodies, are considered to be at lower risk and only advised treatment if they have other risk factors. If they have three other pregnancy risk factors they are advised ante-and postnatal prophylaxis; if they have only two, prophylaxis is advised from 28 weeks of pregnancy; and if they have only one other risk factor, only for 19 days postpartum.[2]

Women with hereditary thrombophilia and past second-trimester loss are also advised thromboprophylaxis as there is evidence it may improve live birth rate. However RCOG found insufficient evidence of an effect in women with previous first trimester loss.[3]

Basis for current recommendation

The most recent UK NSC external review of antenatal screening for thrombophilia conducted in 2010 concluded that universal screening for thrombophilia as a group of conditions, or any individual condition, was not recommended.

This recommendation was primarily based on the largest study in this field, the Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS[1]) health technology appraisal conducted in 2006. The TREATS[1] study aimed to examine the clinical complications associated with thrombophilia during pregnancy; the effectiveness and safety of thromboprophylaxis in these women; and to look at the evidence for screening pregnant women for thrombophilia and then giving thromboprophylaxis to screen-positive women.

The TREATS[1] study concluded that:

- Thrombophilia is associated with increased risk of VTE and other adverse outcomes in pregnancy. However, risk differs by the type of thrombophilia variant. The highest risk association was found for factor V Leiden and VTE. Significant risk associations were found between individual thrombophilia defects and other pregnancy outcomes.
- There is a lack of studies comparing universal screening of all pregnant women with other screening programmes.
- Selective thrombophilia testing based on the presence of VTE risk factors is likely to be more cost effective than universal screening.
- There is insufficient evidence that thromboprophylaxis is effective for preventing pregnancy complications in women with thrombophilia. Large prospective cohorts or trials need to examine whether screening and subsequent treatment leads to improved health outcomes.

The 2010 UK NSC review did not find significant evidence to address the gaps identified in the TREATS[1] study and concluded that screening was not recommended.

Current update review

The current review was prepared by Bazian Ltd in discussion with the UK National Screening Committee. The review considers whether the volume and direction of the evidence produced between 2010 and 2016 indicates that the previous recommendation should be reconsidered.

The thrombophilias considered are:

- Factor V Leiden
- Prothrombin G2021A mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- MTHFR mutation
- Antiphospholipid syndrome or elevated antiphospholipid antibodies
- Hyperhomocysteinaemia
- Acquired APC resistance

Three main criteria were to be considered. These related to the areas the TREATS[1] study identified as needing further research. A particular focus was given to any evidence found for acquired thrombophilia (antiphospholipid syndrome) to respond to patient requests and following discussion of this condition in the House of Lords. The criteria and key questions

planned for review were as Table 1. Table 2 describes the study eligibility for each key question by population, intervention, comparator and outcome (PICO), as applicable. These were set *a priori* at the scoping stage.

Table 1. Key questions for current thrombophilia update review

Criterion	Key Questions (KQ)	# KQ Studies Included
2) The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.	1) What are the risks associated with heritable and acquired thrombophilia in pregnancy?	Not further assessed (as below)
5) There should be a simple, safe, precise and valid screening test.	2) What is the performance of universal screening strategies for thrombophilia in the general pregnant population looking at: a) Different panels of screening tests (e.g. TREATS modelled FVL, prothrombin G20210A, antithrombin, protein C and protein S deficiencies, lupus anticoagulants and anticardiolipin antibodies) a) Tests specifically for antiphospholipid syndrome (e.g. lupus anticoagulant and anticardiolipin antibodies) b) Different timings and frequency of testing during pregnancy	0
10) There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	3) What is the effectiveness and safety of thromboprophylaxis for preventing VTE and adverse pregnancy outcomes in screen-detected women? Looking at: a) different treatments b) timing of treatment c) dose and duration of treatment c) any identified harms/adverse effects	6

Table 2. Study inclusion and exclusion criteria by key question

Key question	Inclusion criteria						Exclusion criteria
	Population	Intervention/Test	Reference Standard	Comparator	Outcome	Study type	
1) What are the risks associated with heritable and acquired thrombophilia in pregnancy?	Pregnant women with thrombophilia	NA	NA	Pregnant women without thrombophilia	VTE (DVT/PE) Miscarriage Stillbirth Pre-eclampsia IUGR Placental-abruption Postpartum-haemorrhage	Comparative prospective cohorts Retrospective cohorts Case controls Systematic reviews of these studies	Cohorts of women with thrombophilia without a comparison group Papers published before 2010, papers not available in English language, letters, editorials, conference abstracts, other grey literature.
2) **Is there a safe, simple, precise and valid screening test**	Non-selected pregnant women (ie. without indications such as VTE themselves , or FH or VTE in a relative <50)	Different panels of screening tests; or those specifically for APS. Different timings and frequency of testing during pregnancy	Detection of women with confirmed thrombophilia; or Detection of those who experience VTE or adverse pregnancy outcomes	NA	Test accuracy: Sensitivity, specificity, PPV, NPV, FPR, FNR	Cohorts of screened populations or systematic reviews of these studies	Non-human studies, papers not available in the English language, letters, editorials and communications, grey literature and conference abstracts.
3) What is the effectiveness and safety of thromboprophylaxis for preventing VTE and adverse pregnancy outcomes in screen-detected women	Screen-detected women (with or without additional risk factors), or asymptomatic women detected by other means	Aspirin LMWH Unfractionated heparin Combination	NA	Placebo Alternative treatment	VTE (DVT/PE) Miscarriage Stillbirth Pre-eclampsia IUGR Placental-abruption Postpartum-haemorrhage	RCTs Prospective cohorts if RCTs not available Systematic reviews of these studies	Studies of women already taking thromboprohylaxis before pregnancy (eg. looking at change to dose or treatment). Non-human studies, papers not available in the English language, letters, editorials and communications, grey literature, conference abstracts and trial protocols.

A systematic literature search of three databases was performed for studies addressing these questions published between January 2010 and 10th June 2016. The search strategy is detailed at the end of this report.

Overall the search yielded 1849 unique references addressing thrombophilia in pregnancy. Of these, 269 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 95 were selected for full text appraisal.

Initial selection and appraisal of studies was predominantly undertaken by one reviewer, with further discussion on inclusions and approach made with a second reviewer and with the UK NSC. Any refinements to the study inclusion criteria as outlined in Table 2, and further information on the evidence selection process for each key question, is discussed in the evidence description for each criterion in the report.

After full literature appraisal and discussion of the evidence with UK NSC, the decision was made not to proceed further with appraisal of Criterion 2 on natural history.

Summary of natural history of thrombophilia in pregnancy

The TREATS[1] study concluded that overall hereditary and acquired thrombophilia are associated with increased risk of VTE and adverse pregnancy complications, but the likelihood of clinical outcomes varies with the underlying condition. Certain mutations are thought to carry higher risks than others.

TREATS[1] found the highest risk association between factor V Leiden and venous thromboembolism, with homozygous carriers having 34 times the risk of VTE compared with non-carriers. Smaller significant risk associations with VTE were also found individually for heterozygous FVL carriage, prothrombin mutation, antithrombin deficiency and protein C and S deficiency. No association was found for MTHFR homozygous. Analyses weren't available for other variants.

TREATS[1] also found associations between specific thrombophilia variants and other individual pregnancy outcomes. Significant risk associations were found for:

- Early pregnancy loss (before 24 weeks): FVL homozygous, prothrombin homozygous, anticardiolipin antibodies and lupus anticoagulant (antiphospholipid antibodies), acquired APC-resistance, hyperhomocysteinaemia
- Later pregnancy loss (after 24 weeks): FVL heterozygous, prothrombin heterozygous, protein S deficiency and anticardiolipin antibodies
- Pre-eclampsia: FVL heterozygous, prothrombin heterozygous, MTHFR homozygous, anticardiolipin antibodies, hyperhomocysteinaemia
- Placental abruption: FVL heterozygous, prothrombin heterozygous, hyperhomocysteinaemia
- IUGR: FVL homozygous, prothrombin heterozygous

The strength of these associations varied, and data was not available for all variants and all outcomes. Nevertheless meta-analyses for each outcome found that presence of any hereditary

or acquired thrombophilia in general increased risk of VTE and each of these other adverse pregnancy outcomes.

We reviewed 65 full texts published since 2010 to see if there is any evidence to update understanding on natural history, in particular addressing any gaps on the associations for rarer hereditary or acquired thrombophilia variants.

We identified four cohort studies and 32 case control studies examining the links between individual variants and any of the pregnancy outcomes of interest.

As the highest level of evidence, the four cohort studies were reviewed first. These were large cohorts of non-selected women who should be representative of screen-detected women, but otherwise the quality of the studies varied. A summary of their methods and findings is presented in Appendix ii.

Only one of these studies had assessed the association with VTE.[5] This retrospective cohort examined the link with antiphospholipid antibodies (aPLs) and found aPLs increased risk of VTE, in addition to increasing risk of pregnancy-induced hypertension and preterm birth. This is broadly consistent with the findings of TREATS[1] (for outcomes where TREATS[1] had data on aPLs available).

The other three prospective cohort studies[6-8] examined FVL and prothrombin mutation with one additionally looking at MTHFR mutations. None had examined VTE outcomes so are not able to confirm or update the association found by TREATS[1].

All three also looked at outcomes of pre-eclampsia, pregnancy loss, placental abruption and SGA baby. The two best quality cohort studies found no significant association between FVL or prothrombin mutation and any of these outcomes. The third lower quality study conversely found that PT heterozygous carriage was associated with increased risk of these outcomes. When these three cohorts were pooled in an earlier meta-analysis[9] there was no significant association found for prothrombin mutation, with only a single significant association found between FVL and pregnancy loss.

These findings therefore broadly conflict with the associations found by TREATS[1]. However, TREATS[1] had also found fairly inconsistent risk associations depending on whether it was heterozygous or homozygous FVL or PT carriage. TREATS[1] had separately examined pregnancy loss by trimester, which these studies hadn't, and examined IUGR as the outcome rather than SGA baby. TREATS[1] had also considered a much larger body of evidence, including mostly case-control studies.

In terms of updating the TREATS[1] study, the evidence from these four new cohort studies created a complicated picture. There was consistency in relation to some associations and inconsistency in relation to others. Alone these studied seemed insufficient to draw firm conclusions.

The four studies were very limited in terms of furthering understanding of thrombophilia as recommended by the TREATS[1] study. They did not provide updated evidence for any of the other hereditary or acquired thrombophilia variants for which the TREATS[1] found adverse associations.

To assess natural history further would require examination of the 32 case control studies identified by the literature search. These looked at the presence of a range of thrombophilia variants in women with and without a range of different adverse pregnancy outcomes.

A systematic review on natural history that updates the TREATS[1] meta-analyses and pools all observational evidence to date for each hereditary and acquired thrombophilia variant, and for each adverse pregnancy outcome, may be valuable for this purpose. This was beyond the scope of this evidence summary. In addition the assessment of evidence relating to the key questions on the test and intervention suggested that universal population screening was not well supported by the evidence.

Given this situation a decision was taken in discussion with UK NSC not to proceed with assessment of natural history at the current time.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

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

Description of the previous UK NSC evidence review conclusion

The TREATS[1] study and the last UK NSC review both noted the lack of studies examining universal antenatal screening programmes for thrombophilia, particularly in low risk women without additional risk factors. This may be because it is not thought not to be cost effective or appropriate as many hereditary and acquired thrombophilias, such as carriage of antiphospholipid antibodies, are associated with a low risk of adverse outcomes in women without additional risk factors and so would not indicate treatment.

The review also noted the range of assays available to test for the different thrombophilias, and the inconsistency across UK labs in the variants they test for. Most commonly tests were reported to include factor V Leiden, and proteins C and S deficiency. Reference ranges are available for adults, with test results usually described as "normal" or "low", or "positive" or "negative".

Current UK NSC key question

Current guidance recommends antenatal thrombophilia testing only in women with a personal history of unprovoked or oestrogen-associated VTE, women with second trimester pregnancy loss, or in asymptomatic women with a family history of VTE (unprovoked or oestrogen-associated) before the age of 50.

The TREATS[1] study modelled the strategy of universal screening of all women at the onset of pregnancy (six weeks' gestation). This assumed that a screening panel would include FVL, prothrombin mutation, deficiencies of antithrombin, protein C and protein S, lupus anticoagulants and anticardiolipin antibodies. The study also modelled selective screening based on personal or family history of VTE. All screen-positives were assumed to receive pregnancy thromboprophylaxis. The probabilities of adverse pregnancy outcomes were derived from systematic review and healthcare costs compared. TREATS[1] concluded that selective screening based on prior VTE history was more cost effective than universal screening. Because of the absence of primary screening studies it concluded that future studies need to compare the clinical effectiveness of universal screening with other healthcare programmes.

The current review aimed to see whether there is new evidence evaluating universal screening strategies for all pregnant women, regardless of risk factors, compared with either no screening, or selective screening based on the presence of risk factors. The search strategy sought studies evaluating different panels of screening tests, or those looking at screening for individual variants such as antiphospholid antibodies.

The last NSC review noted that tests with good analytical validity for thrombophilias are available, but no studies had explored the use of these tests for the purposes of screening the general pregnant population without risk factors. Therefore priority was given to identifying prospective studies that compared universal thrombophilia screening strategies (for any or all variants) with no screening or with selective testing, and which reported test performance

measures (e.g. negative and positive predictive value) for identifying women at risk women of adverse pregnancy outcomes. Studies that specifically informed on the most reliable screen tests and cut-off values to use and the timing of screening during pregnancy would also be valuable.

Description of the evidence

Few studies of potential relevance to this question were identified at abstract screening. Fourteen studies were selected for more in-depth full text review. No studies met the eligibility criteria for this key question at full text appraisal.

No trials or cohort studies were identified that had assessed universal antenatal thrombophilia screening in the general pregnant population.

One study[10] assessed the screening performance of self-reported family history of VTE (first- or second-degree relative) to predict an asymptomatic woman being a carrier of factor V Leiden mutation. However, selective hereditary thrombophilia testing based on family history is already recommended practice.

One decision analysis model of universal antenatal screening was also identified.[11] This study compared a strategy of screening women with prior adverse pregnancy outcome (pre-eclampsia, recurrent pregnancy loss, fetal growth restriction, fetal death or preterm birth) with no screening. The model analysed the probability of different outcomes, for example true positive/true negative and good/bad pregnancy outcomes as informed by a literature review. This study therefore considers a testing strategy in high-risk pregnancies only, rather than universal screening of all women.

We further excluded studies assessing:

- the validity of new diagnostic assays for diagnosing thrombophilia compared with the standard assay
- blood coagulation parameters, but not looking at any specific thrombophilia variants
- thrombophilia screening specifically for women undergoing assisted reproductive technologies (ART)
- thrombophilia screening for women being considered for the oral contraceptive pill, or other non-pregnancy screening
- screening of asymptomatic relatives of probands with thrombophilia

Summary: Criterion 5 not met.

Evidence required to answer this key question was not identified by the literature search. Since the last evidence review no studies have been published that have evaluated a strategy of universal screening of all pregnant women for any thrombophilia variant, either compared with no screening or selective testing. In the absence of such studies, it is not possible to evaluate whether there is a benefit to be gained from universal screening of the general pregnant population compared with current practice of selective testing.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

Description of the previous UK NSC evidence review conclusion

The previous NSC review found research suggesting that identifying hereditary thrombophilia would not usefully influence management as thromboprophylaxis would normally only be indicated if the woman had additional risk factors, was homozygous or had more than one mutation.

In the UK, RCOG treatment recommendations are based on the different risk associated with the different variants. Antenatal and postnatal thromboprophylaxis is advised for those with antithrombin, protein C or S deficiency, homozygous for other variants, or compound heterozygotes.[2] Women who are heterozygous for factor V Leiden or prothrombin gene mutation, or who have antiphospholipid antibodies, are considered at lower risk and only advised prophylaxis if they have additional pregnancy risk factors.[2]

Women with a hereditary thrombophilia and past second-trimester loss are also recommended thromboprophylaxis as there is evidence that it may reduce risk of recurrent late pregnancy loss.[3]

Current UK NSC key question

This review aimed to look for evidence on the effectiveness and safety of management and thromboprophylaxis for women with thrombophilia who would be detected through universal screening. Outcomes of interest were VTE and other pregnancy morbidity, for example early or late pregnancy loss, IUGR/SGA baby, placental abruption or postpartum haemorrhage.

The aim was to prioritise RCTs or, if these were not available, prospective comparative cohort studies where additional pregnancy risk factors aside from thrombophilia where not a prerequisite to inclusion. Therefore the population could be most representative of all women with thrombophilia detected through screening, regardless of prior pregnancy complications. Non-comparative cohorts, that only reported outcomes in treated women, would be excluded.

Description of the evidence

Overall 59 studies were identified as potentially relevant during title and abstract sifting and 22 were assessed at full text.

No RCTs or prospective comparative cohort studies of screen-detected women with hereditary or acquired or thrombophilia were identified. Neither were there any RCTs or comparative cohorts that included a non-selected group representative of all women with thrombophilia, regardless of additional risk factors, and compared outcomes in those treated and not treated.

All identified comparative studies included women with thrombophilia who had additional pregnancy-related risk factors.

The previous UK NSC review noted that some ongoing RCTs were due to report and that these may be relevant for future reviews. These included the FRUIT study and TIPPS study. For completion a decision was made to consider the evidence from randomised controlled trials that included women with thrombophilia and additional risk factors, or systematic reviews of these RCTs.

We excluded systematic reviews where all included RCTs pre-dated 2010[12-16] as this evidence would have been considered by the last external UK NSC review. This included two reviews examining the effect of aspirin in women with antiphospholipid antibodies (aPLs), but there were additional methodological limitations to both of these reviews due to the variable quality of evidence pooled. One review[12] specifically examined women with aPLs who did not have a diagnosis of APS, meta-analysing the results of two pre-2010 RCTs and one 2013 retrospective cohort. This latter study was excluded from the current evidence appraisal on account of the retrospective study design. The second review[13] pooled 10 cohorts (a mixture of prospective and retrospective), and only a single pre-2010 RCT. The post-2010 cohorts in this review were identified by the current search but were also excluded from this appraisal on account of their study design.

We excluded systematic reviews where the trial population was heterogeneous and included women with or without thrombophilia, without giving separate analysis of women with thrombophilia only.[17, 18] It was not possible to access the full text for one potentially relevant patient data meta-analysis examining the effect of LMWH on placenta-mediated complications.[19]

We excluded RCTs examining the effect of thromboprophylaxis on the outcomes from assisted reproduction, those examining the effect of pre-conception treatment (which would be irrelevant to antenatal screen detection), and those otherwise examining thrombophilia treatment outside of pregnancy.

We also excluded two studies from non-OECD countries. This included one RCT comparing two doses of LMWH in high risk women (20mg vs. 40mg)[20] and another where the study design was questionable with a high risk of bias around randomisation and allocation concealment.[21]

Six studies met the revised inclusion criteria, including two key RCTs and three systematic reviews (Table 3). The TIPPS RCT[22] compared LMWH with no LMWH in women with hereditary or acquired thrombophilia and high-risk criteria for pregnancy complications. The FRUIT RCT compared LMWH plus aspirin vs. aspirin alone in women with hereditary thrombophilia[23] or antiphospholipid antibodies[24] and prior pregnancy hypertension and SGA baby.

The three systematic reviews all focused on the effect of treatment on live birth rate. These SRs pooled the results of additional post-2010 RCTs which have therefore not been separately analysed here. Zhang et al. (2015)[25] performed a standard and network meta-analysis comparing the effect of different forms of thromboprophylaxis in women with prior recurrent pregnancy loss. Only the analysis of women with APS is presented here, as the analysis of hereditary thrombophilia included a pooled population of women with or without hereditary thrombophilia and it was not possible to separate out the effect in women with hereditary thrombophilia.

The two remaining SRs covered women with hereditary thrombophilia, but with slightly different inclusion criteria. Areia et al. (2016)[26] examined the effect of LMWH plus aspirin vs. aspirin alone in women with hereditary thrombophilia. Their search criteria didn't specify that women had to have additional risk factors, but all of their identified trials included women with risk factors (mostly prior pregnancy loss). Skeith et al. (2016)[27] examined LMWH (+/-aspirin) vs. no LMWH (+/-aspirin) and specified that their search was to include women with hereditary thrombophilia and recurrent or late pregnancy loss. Therefore there was some overlap in the trials covered by these reviews.

Results

Table 3: RCTs and SRs of thromboprophylaxis in pregnant women with hereditary or acquired thrombophilia plus additional risk factors

Study	Design/Setting	Population	Intervention	Comparator	Outcomes
Roger et al. 2014[22] "TIPPS" Appendix 1	Single blind RCT (assessors) 36 centres in US, Canada, UK, France	N=292 women with • FVL/APC-R, PT mutation, protein C or S or AT deficiency, or aPLs; *plus* • high risk criteria (prior pre-eclampsia, SGA baby, placental abruption, pregnancy loss, or VTE risk factors)	LMWH (dalteparin 5000 IU once daily to wk 20, twice daily to 37 wks)	No treatment	**Composite of VTE, pre-eclampsia, SGA baby or pregnancy loss** - ns LMWH 17.1% vs. control 18.9%; difference -1.8% (95% CI -10.6 to 7.1); p=0.70 Secondary outcomes: non-significant for VTE, pre-eclampsia, pregnancy loss, placental abruption, SGA baby or preterm birth. Significant for minor bleeding only: LMWH 19.6% vs. control 9.2%; p=0.01
de Vries et al. 2011[23] "FRUIT" Appendix 2	Open label RCT Multiple centres in the Netherlands, two in Australia and one centre in Sweden.	N=139 • FVL/APC-R, PT mutation, protein C or S deficiency; *plus* • prior pregnancy hypertension and delivery of SGA baby	LMWH + aspirin (dalteparin 5000 IU plus 80-100mg aspirin daily 6-12 to 36 wks gestation)	Aspirin	**Hypertension of pregnancy <34 weeks** LMWH 0% vs. control 8.7%; RD 8.7% (95% CI 1.9 to 15.5); p=0.012 **Irrespective of gestational age** - ns LMWH 18.6% vs. control 21.7%; RD 3.1% (95% CI -10.5 to 16.7); p=0.642 Secondary outcomes: significant for pre-eclampsia before 34 wks only; ns for all pre-eclampsia, HELLP, SGA baby, pregnancy loss, preterm birth. Significant for overall side effects (LMWH 12.9 vs. control 2.9%); only skin reaction specifically (11.4% vs. 0).
Van Hoorn et al.		N=32			**Hypertension of pregnancy <34**

2016[24] Appendix 3		• aPLs; *plus* • prior pregnancy hypertension and delivery of SGA baby			**weeks** - ns LMWH 0 vs. 6.3%; RD 6.25% (95% CI -17 to 27); p=0.310 **Hypertension of pregnancy irrespective of gestation** - ns LMWH 0 vs. 12.5%; RD 12.5% (95% CI -15 to 35); p=0.144 All other secondary outcomes also ns
Zhang et al. 2015[25] Appendix 4	Systematic review with pair-wise (PW) and network (NW) meta-analysis	N=543, 6 RCTs • APS; *plus* • recurrent pregnancy loss	LMWH	Aspirin	**Live birth rate** PW: OR 2.42 (95% CI 1.04 to 5.66) NW: OR 2.42 (95% CI 1.09 to 5.62)
			UFH + aspirin	Aspirin	PW: OR 2.47 (95% CI 1.36 to 4.52) NW: OR 2.54 (95% CI 1.54 to 4.31)
			Aspirin	Placebo	PW and NW - ns
			LMWH	Placebo	NW ns (PW na)
			LMWH + aspirin	Placebo	NW ns (PW na)
			UFH + aspirin	Placebo	NW ns (PW na)
			LMWH + aspirin	Aspirin	PW and NW - ns
			LMWH + aspirin	LMWH	NW ns (PW na)
			UFH + aspirin	LMWH	NW ns (PW na)
			UFH + aspirin	LMWH + aspirin	PW and NW - ns
Areia et al. 2016[26] Appendix 5	SR and MA	N=222, 4 RCTs • hereditary thrombophilia (all RCTs included women with additional risk factors: RPL in 3, hypertension in 1)	LMWH + aspirin	Aspirin	**Live birth rate** - ns OR 1.70 (95% CI 0.72 to 4.00)

Skeith et al. 2016[27] Appendix 6	SR and MA	N=483, 8 RCTs • hereditary thrombophilia; plus • recurrent or late pregnancy loss	LMWH +/- aspirin	No LMWH +/- aspirin	**Live birth rate** - ns All trials: RR 0.81 (95% CI 0.55 to 1.19) Multicentre trials: RR 1.04 (95% CI 0.93 to 1.16)

Abbreviations: aPLs, antiphospholipid antibodies; APS, antiphospholipid syndrome; AT, antithrombin; CI, confidence interval; FVL, factor V Leiden; FRUIT, FRactionated heparin in pregnant women with history of Uteroplacental Insufficiency and Thrombophilia; HELLP, haemolysis, elevated liver enzymes and low platelets; LMWH, low molecular weight heparin; na, not available; ns, non-significant; OR, odds ratio; PT, prothrombin; RD risk difference; RPL, recurrent pregnancy loss; RR, relative risk; SGA, small for gestational age; TIPPS, thrombophilia in pregnancy prophylaxis study; UFH, unfractionated heparin.

The main limitation of the body of evidence on thromboprophylaxis is the limited applicability to all screen-detected women. The women included by these RCTs all had additional risk factors for pregnancy complications. There is a current recommendation to treat women with hereditary variants or antiphospholipid antibodies if they have certain additional risk factors, such as past VTE, pre-eclampsia or second trimester loss. Therefore many of the women included by these studies would already meet current criteria for treatment.

In terms of population characteristics, the trials included women with variable pregnancy-related risk factors and thrombophilia variants. TIPPS[22] included women with any hereditary or acquired thrombophilia – both hetero- and homozygotes – though they excluded those with APS and history of RPL (on the grounds that this was an indication for treatment). FRUIT[23] excluded women homozygous for factor V Leiden or prothrombin mutation, and women with antithrombin deficiency. In the Zhang et al. [25] meta-analysis it is not known whether or not women met diagnostic criteria for APS.

Given this variability it is difficult to generalise these results to a low risk population of all women with screen-detected thrombophilia.

Even in high risk women, the trials provide inconsistent results on the effectiveness of thromboprophylaxis. In the main there was no evidence that treatment was effective with the exception of isolated significant findings for LMWH + aspirin vs. aspirin alone on the outcome of recurrent hypertension below 34 weeks in women with hereditary thrombophilia (FRUIT[23]); and LMWH or UFH + aspirin compared with aspirin alone on the outcome of live birth rate in women with APS and recurrent pregnancy loss (Zhang et al.[25]).

The doses of LMWH in the trials and the time of treatment initiation also varied. For example, the TIPPS[22] trial doubled the dose of LMWH from 20 weeks onwards, while FRUIT[23, 24] did not. The TIPPS[22] trial also included women who were on average at 12 weeks' gestation at the time of randomisation, while FRUIT[23, 24] required women to be <12 weeks' at randomisation and started treatment around 6-12 weeks. Earlier treatment during the first trimester may have different effect. In a screening context, initiation of treatment would depend on the timing of screening, which no studies are able to inform.

The comparators also varied widely across trials. TIPPS[22] included a LMWH vs. no treatment comparison, while FRUIT[23, 24] had no comparison to untreated women, looking at LMWH + aspirin vs. aspirin. The reviews by Areia et al.[26] and Skeith et al.[27] included mostly women with hereditary thrombophilia and prior pregnancy loss, but pooled a different selection of trials on account of their different comparisons – LMWH plus aspirin, or more broadly with/without aspirin. More standardised interventions and comparators would be beneficial.

The Zhang et al.[25] review did attempt to evaluate the effect of different treatment combinations, but this is limited not only by the specific population (women with APS and RPL) but the small number of trials and the lack of direct comparisons. Despite significant findings for LMWH or UFH + aspirin compared with aspirin, no effect was found when these treatments were compared with placebo. However, there was only one placebo-controlled trial in the group (aspirin vs. placebo), so all other no-treatment comparisons were indirect.

The outcomes measured by the reviews/trials also represent only a limited number of the adverse outcomes potentially associated with thrombophilia. VTE was not a primary outcome in any of these trials, only being covered in the composite outcome of the TIPPS[22] trial.

More information is also needed on the adverse effects of thromboprophylaxis. TIPPS[22] found significantly higher rates of minor bleeding with LMWH, FRUIT[23] with skin reaction only. The systematic reviews noted the inconsistency in reporting of adverse effects across trials.

The heterogeneity of trials in terms of the populations studied (thrombophilia variants, additional risk factors), treatments, comparators and pregnancy outcomes makes them difficult to compare directly and give any overall summary on effect of treatment.

Summary: Criterion 10 not met.

Overall, the studies required to answer the key question were not identified in the literature. All of the identified trials were in women with other pregnancy-related risk factors. The trials were also collectively heterogeneous in terms of thrombophilias assessed; type and dose of thromboprophylaxis and timing of initiation; comparators; and pregnancy outcomes assessed. Consequently the findings were inconsistent across trials. Safety data was also insufficient.

The review finds an absence of evidence to answer whether management and treatment of all women with thrombophilia identified through screening would improve pregnancy outcomes.

Conclusions

Implications for policy

This report assesses antenatal thrombophilia screening against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

This review sought to establish whether evidence relating to key questions suggests that the current recommendation not to screen for thrombophilia in pregnancy should be reconsidered.

No studies were identified that assessed universal thrombophilia screening of all pregnant women compared with either no screening, or current practice of selective testing based on risk factors. Neither was any evidence available to inform on the clinical validity and utility of any screening tests, cut-offs to use or timing of screening.

RCTs have been published that have reviewed the effectiveness of thromboprophylaxis in women with hereditary thrombophilia or antiphospholipid antibodies, but all of these trials included women with additional pregnancy risk factors, such as prior pregnancy loss, pre-eclampsia or baby born small for gestational age. Many of these women would meet current treatment criteria. There was no evidence to inform on the effectiveness and safety of management and treatment strategies in populations representative of all screen-detected women.

Overall the evidence required to inform on a universal antenatal screening programme for thrombophilia has not been published since 2010, which indicates that current recommendation not to screen in the UK should not be reconsidered at the present time.

These issues are unlikely to be resolved without further research in the following areas:

- Large prospective studies that compare universal thrombophilia screening of all pregnant women either with no screening or with current practice of selective testing based on risk factors, and that examine the effect on adverse pregnancy outcomes.
- Prospective studies that inform on the clinical performance of different panels of screening tests, or those specifically for antiphospholipid antibodies, and inform on the optimal timing of antenatal testing
- Randomised controlled trials that assess the effectiveness and safety of thromboprophylaxis in women with hereditary or acquired thrombophilia who are not selected on the basis of additional risk factors and so would be representative of all screen-detected women
- A systematic review with meta-analysis to update the epidemiological evidence from the TREATS[1] 2006 and explore the adverse pregnancy outcomes that are associated with each of the hereditary and acquired thrombophilia variants.

Limitations of the rapid review process

This was a rapid review conducted over a period of eight weeks. It was guided by a protocol developed *a priori* which covered only three key questions where the previous UK NSC review had noted uncertainty.

Literature search and first pass appraisal were predominantly undertaken by one information specialist, and second pass appraisal and study selection by one analyst. Any queries at both stages, including any revisions to inclusion or exclusion criteria set *a priori*, were resolved through discussion with a second analyst and with UK NSC.

We limited our searching to three bibliographic databases and did not search grey literature sources. In our search appraisal we prioritised systematic reviews before sifting through the lower levels of primary literature. We used standard, systematic approaches for study selection, data extraction, and validity assessment.

We did not include studies available only in non-English language, and did not review abstracts, conference reports or poster presentations. We were also unable to contact study authors or review non-published material given the timeframe. We were unable to locate the full text report for one potentially relevant article.

We considered only the literature published over the past six years. This involved the exclusion of systematic reviews that pooled evidence from pre-2010 studies only as these would have been considered by the previous external review.

Due to the constraints of the evidence summary, and indications from appraisal of Criteria 5 and 10 that universal screening would not be indicated, we did not proceed with full appraisal of the large body of relevant literature identified on epidemiology.

As such this does not represent a comprehensive systematic review of all evidence related to the topic.

Methodology

The draft update report was prepared by Bazian Ltd.in discussion with the UK National Screening Committee. The review was conducted in keeping with the UK NSC requirements for evidence

summaries using rapid review methodologies. 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 assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables. The review was checked within Bazian Ltd's quality assurance process.

Search strategy

The searches for the three key questions were conducted in the MEDLINE and Embase databases via Embase.com. The following Cochrane Library databases were also searched: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, and Database of Abstracts of Reviews of Effect. The searches started from 2010 (the publication date of the initial review). Searches were undertaken on 10th June 2016. English language limit was applied to the searches. Methodological search filters were not used. A copy of the search strategies used in the major databases is as follows. The database searches identified 1849 unique records.

Search strategy for MEDLINE and Embase (Embase.com)

Search strategies were developed for MEDLINE and Embase (Embase.com) and were adapted appropriately for the databases searched via the Cochrane Library (Wiley).

Searches	Query	Results
1	'thrombophilia'/de	10,087
2	'activated protein c resistance'/de OR 'antithrombin iii deficiency'/de OR 'hypercoagulability'/exp OR 'protein c deficiency'/de OR 'protein s deficiency'/de OR 'blood clotting factor 5 leiden'/de OR 'hyperhomocysteinemia'/de OR 'antiphospholipid syndrome'/de	36,743
3	thrombophil*:ab,ti OR hypercoagula*:ab,ti	20,404
4	'apc resistance':ab,ti OR 'activated protein c resistance':ab,ti	1,898
5	'factor v leiden':ab,ti OR 'factor 5 leiden':ab,ti	5,340
6	'prothrombin g2021a':ab,ti	3
7	('protein c' NEAR/3 deficiency):ab,ti	2,036
8	('protein s' NEAR/3 deficiency):ab,ti	1,686
9	(antithrombin NEAR/5 deficiency):ab,ti	1,775
10	mthfr:ab,ti OR methylenetetrahydrofolate:ab,ti	8,816

11	'antiphospholipid syndrome':ab,ti OR 'hughes syndrome':ab,ti OR 'elevated antiphospholipidantibodies':ab,ti	8,627
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	57,481
13	'pregnancy'/exp OR 'pregnancy complication'/exp OR 'pregnancy outcome'/de	704,372
14	antenatal:ab,ti OR 'ante natal':ab,ti OR antepartum:ab,ti	41,421
15	prenatal:ab,ti OR 'pre natal':ab,ti OR prepartum:ab,ti	94,852
16	maternal:ab,ti OR obstetric*:ab,ti	328,809
17	pregnan*:ab,ti	519,453
18	#13 OR #14 OR #15 OR #16 OR #17	1,034,089
19	#12 AND #18	9,793
20	'prenatal diagnosis'/exp OR 'mass screening'/de OR 'prenatal screening'/de OR 'screening test'/de	194,108
21	'maternal serum screening test'/de	149
22	test:ab,ti OR tests:ab,ti OR testing:ab,ti	2,340,906
23	screen*:ab,ti OR detect*:ab,ti OR diagnos*:ab,ti	4,899,678
24	'predictive value'/de OR 'sensitivity and specificity'/de OR 'diagnostic accuracy'/de	455,698
25	'predictive value':ab,ti OR 'sensitivity and specificity':ab,ti OR 'diagnostic accuracy':ab,ti	197,007
26	#20 OR #21 OR #22 OR #23 OR #24 OR #25	6,648,429
27	#19 AND #26	4,617
28	'anticoagulant agent'/exp OR 'heparin'/de OR 'acetylsalicylic acid'/de	553,375
29	anticoagula*:ab,ti OR heparin:ab,ti OR ufh OR lmwh OR aspirin:ab,ti	223,079
30	thromboprophyla*:ab,ti OR prophyla*:ab,ti OR antithrombotic:ab,ti	212,445
31	#28 OR #29 OR #30	688,661

32	#19 AND #31	5,541
33	#27 OR #32 AND [english]/lim AND [2010-2016]/py	3,623
34	#27 OR #32 AND [english]/lim AND [2010-2016]/py AND [conference abstract]/lim	1,810
35	#33 NOT #34	1,813

Appendix i

Appendix number	1
Relevant criteria	10
Publication details	Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): A multinational open-label randomised trial. The Lancet. 2014;384(9955):1673-83.[22]
Study details	Single blind RCT, multicentre (36 tertiary centres in Canada, USA, Australia, UK, France – recruitment from 21), 2000 to 2012
Study objectives	To see whether antenatal prophylactic LMWH (dalteparin) reduced risk of VTE and pregnancy-related complications in women with thrombophilia and high risk of pregnancy complications
Inclusions	Pregnant women with confirmed diagnosis of thrombophilia (factor V leiden [or APC-R and a first degree relative with FVL] or prothrombin gene mutation [both hetero- or homozygous], protein C deficiency, protein S deficiency, antithrombin deficiency, antiphospholipid antibodies [≥2 positive tests for ≥1 of anticardiolipin, anti-β2 glycoprotein or lupus anticoagulant]); plus one or more high risk criteria (prior pre-eclampsia, SGA baby, placental abruption, pregnancy loss, VTE events/risk factors)
Exclusions	≥21 weeks' gestation at recruitment; contradiction to heparin; indication for thromboprophylaxis (including APS and RPL, prior unprovoked VTE; on long-term anticoagulation before pregnancy) geographical inaccessibility; prior participation in TIPPS trial; below age to give informed consent.
Population	N=292. Average age 31; 37% smokers; BMI 27; FVL (64% intervention/57% controls), PT mutation (21%/23%), Protein S (8%/9%), Protein C (4%/8%), AT deficiency (1%/1%); APL antibodies (8%/7%); VTE events/risk factors (46%/43%); other past pregnancy complications (63%/59%); 12 wks gestation at randomisation
Intervention	Antenatal dalteparin 5000 IU once daily to 20 weeks, twice daily to 37 weeks (n=146)
Comparator	No treatment (n=143) (both groups prescribed postnatal dalteparin 5000 IU once daily to day 42)

Results/outcomes	Primary outcome – composite of VTE (DVT, PE or sudden maternal death); severe or early onset (<32 wks) pre-eclampsia; SGA baby (<10th percentile); pregnancy loss: • no difference between groups: LMWH 17.1% (25) vs. control 18.9% (27); difference -1.8% (95% CI -10.6 to 7.1); p=0.70 Secondary outcomes: • VTE (ns) • SGA baby (ns) • Pregnancy loss (ns) • Pre-eclampsia (ns) • major bleeding (ns) • minor bleeding: LMWH 19.6% (28) vs. control 9.2% (13); p=0.01 • thrombocytopenia, change in bone mineral density or osteoporotic fractures (no events)
Comments	Single blind – participants, outcome assessments blinded. Low risk of bias around randomisation or treatment allocation. Adequately powered: 284 needed for 80% power to detect minimal clinically important difference (16%) in primary outcome. ITT analysis. No participants lost to follow-up but 3.4% non-compliant with LMWH dose, and 26 crossed over to the opposite treatment group (12 and 14 in each group). Generalisable and applicable to UK setting, but main limitation in applicability to asymptomatic screen-detected women – pre-requisite of high risk criteria, though people with indications for thromboprophylaxis (including APS and RPL) were excluded. Unable to assess whether there could be an effect of LMWH when combined with aspirin – used by 30% of intervention and 40% of control group. 12 weeks of pregnancy at randomisation – earlier treatment may have different effect.

Appendix number	2
Relevant criteria	10
Publication details	de Vries JIP, van Pampus MG, Hague WM, et al. Low-molecular-weight heparin

	added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: The FRUIT-RCT. Journal of Thrombosis and Haemostasis. 2012;10(1):64-72.[23]
Study details	Open label RCT, Multicentre (across Netherlands, 2 centres in Australia, 1 in Sweden, start date 2000 to 2009
Study objectives	To test whether adding LMWH to aspirin prior to 12 weeks' gestation reduces recurrence of hypertension in women with hereditary thrombophilia with previous early onset hypertension of pregnancy and SGA baby
Inclusions	Pregnancy <12 weeks; hereditary thrombophilia (FVL or prothrombin mutation [both heterozygous], protein C or S, APC-R); and history of hypertension of pregnancy (pre-eclampsia, HELLP syndrome, or eclampsia) and delivery of SGA baby <34 weeks' gestation
Exclusions	<18 years, antithrombin deficiency, homozygosity for FVL or PT mutation, diabetes, cancer, peptic ulcer, renal or hepatic insufficiency, history of VTE, thrombocytopenia, bleeding diathesis, use of LMWH in prior pregnancy.
Population	N=139. Age 29, BMI 26, FVL (54% intervention/64% controls), PT mutation (33%/12%), Protein S (17%/17%), Protein C (4%/6%); hyperhomocysteinaemia (15%/17%), chronic hypertension (23%/17%)
Intervention	LMWH (dalteparin 5000 IU) plus aspirin daily (80mg in Netherland centres, 100mg in Australia, 75mg in Sweden) commenced at 6-12 weeks' gestation and continued to 36 weeks. (n=70)
Comparator	Daily aspirin alone (n=69)
Results/outcomes	Primary – reduction in hypertension of pregnancy (pre-eclampsia and/or HELLP and/or eclampsia): • before 34 weeks: LMWH 0 vs. control 8.7% (6); RD 8.7% (95% CI 1.9 to 15.5%); p=0.012 • irrespective of gestational age: NS: LMWH 18.6% (13) vs. control 21.7% (15); RD 3.1% (95% CI -10.5 to 16.7); p=0.642 Secondary outcomes: • Pre-eclampsia <34 weeks: 0 vs. 8.7% (6); p=0.012 • Any pre-eclampsia (ns) • SGA baby (ns) • Pregnancy loss (ns) • Preterm birth (ns)

	• HELLP (ns) • Placental abruption (ns) • Any side effects: 12.9% vs. 2.9%; p=0.03 (specifically skin reaction significant 11.4% vs. 0; all others NS)
Comments	Unblinded study – participants and assessors aware of treatment. Low risk of bias around randomisation or treatment allocation. Adequately powered: 128 needed for 80% power to detect a 50% reduction on a 35% hypertension recurrence rate. ITT analysis. Per-protocol analysis and removal of incorrect trial inclusions (analysis of 66 vs. 65) didn't alter significance of the primary outcome Generalisable and applicable to UK setting, but main limitation in applicability to asymptomatic screen-detected women – pre-requisite of prior hypertension and SGA baby. Also excluded antithrombin deficiency and homozygosity. No control group receiving no treatment for comparison.

Appendix number	3
Relevant criteria	10
Publication details	Van Hoorn ME, Hague WM, Van Pampus MG, et al. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: The FRUIT-RCT. European Journal of Obstetrics Gynecology and Reproductive Biology. 2016;197:168-73.[24]
Study details	Open label RCT, Mutlicentre (across Netherlands, 2 centres in Australia, 1 in Sweden, start date 2000 to 2009
Study objectives	To test whether adding LMWH to aspirin prior to 12 weeks' gestation reduces recurrence of hypertension in women with acquired thrombophilia with previous early onset hypertension of pregnancy and SGA baby
Inclusions	Pregnancy <12 weeks; antiphospholipid antibodies (anticardiolipin or lupus anticoagulant confirmed on at least two occasions); and history of hypertension of pregnancy (pre-eclampsia, HELLP syndrome, or eclampsia) and delivery of SGA baby <34 weeks' gestation
Exclusions	<18 years, antithrombin deficiency, homozygosity for FVL or PT mutation, diabetes, cancer, peptic ulcer, renal or hepatic insufficiency, history of VTE, thrombocytopenia, bleeding diathesis, use of LMWH in prior pregnancy, inclusion in the hereditary FRUIT trial.

Population	N=32. Age 29, BMI 26, chronic hypertension (25%), other hereditary thrombophilia disorder (27% intervention, 43% control) – heterozygous FVL (13%, 29%), protein S (7%/7%).
Intervention	LMWH (dalteparin 5000 IU) plus aspirin daily (80mg in Netherland centres, 100mg in Australia, 75mg in Sweden) commenced at 6-12 weeks' gestation and continued to 36 weeks. (n=16)
Comparator	Daily aspirin alone (n=16)
Results/outcomes	Primary – reduction in hypertension of pregnancy (pre-eclampsia and/or HELLP and/or eclampsia): • before 34 weeks: LMWH 0 vs. control 6.3% (1); RD 6.25% (95% CI -17 to 27%); p=0.310 • irrespective of gestational age: LMWH 0 vs. control 12.5% (2); RD 12.5% (95% CI -15 to 35); p=0.144 Secondary outcomes: • Pre-eclampsia <34 weeks: (ns) • Any pre-eclampsia (ns) • SGA baby (ns) • Pregnancy loss (ns) • Preterm birth (ns) • HELLP (ns) • Placental abruption (ns) • Side effects (ns)
Comments	Unblinded study – participants and assessors aware of treatment. Low risk of bias around randomisation or treatment allocation but small, underpowered study. ITT analysis and all received treatment as allocated. However, inclusion of women with hereditary thrombophilia – 4 in the intervention and 6 in the control group – who researchers report should have been included in FRUIT. 6 week interval between antibody tests was based on 1999 criteria; later 2006 criteria suggest it should be increased to 12 weeks. Also lower aPL antibody threshold for inclsiion than that for diagnosis of APS. Generalisable and applicable to UK setting, but main limitation in applicability to asymptomatic screen-detected women – pre-requisite of prior hypertension and

	SGA baby. No control group receiving no treatment for comparison.

Appendix number	4
Relevant criteria	10
Publication details	Zhang T, Ye X, Zhu T, et al. Antithrombotic Treatment for Recurrent Miscarriage. Medicine (United States). 2015;94(45):e1732.[25]
Study details	Systematic review with pair-wise and network meta-analysis.
Study objectives	To evaluate the effects of different anti-thrombotic treatments on the prevention of recurrent pregnancy loss (RPL) in women with APS and those without apparent cause of RPL other than thrombophilia.
Inclusions	RCTs investigating any anti-thrombotic treatment compared with other treatment or placebo in women with history of ≥2 previous pregnancy losses and with APS or without apparent cause of RPL other than thrombophilia, and reporting live birth rate as the primary outcome. Search date May 2015, PubMed and EMBASE.
Exclusions	22/41 potentially eligible studies not meeting inclusion criteria, including those comparing different types or doses of LMWH; using prednisolone, immunoglobulin or fish oils; and those not specifying reason for RPL.
Population	6 RCTs in women with RPL and APS • N= 543: 80 LMWH, 232 aspirin, 103 LMWH + aspirin, 108 UFH + aspirin, 20 placebo. 12 RCTs in women with RPL with or without thrombophilia: • N=2391: 801 LMWH, 362 aspirin, 388 LMWH + aspirin, 840 placebo or surveillance. 1 RCT covered both populations. All studies included women investigated for thrombophilia with cause of RPL reported as thrombophilia, APS or unknown – though test results or criteria for diagnosis unclear.
Intervention/test	Any anti-thrombotic treatment
Comparator	Alternative treatment, placebo or control
Results/outcomes	<u>Women with APS</u> Significant for:

	• LMWH vs. aspirin: Pair-wise [PW] OR 2.42 (95% CI 1.04 to 5.66), Network [NW] OR 2.42 (95% CI 1.09 to 5.62) • UFH + aspirin vs. aspirin: PW 2.47 (1.36 to 4.52), NW 2.54 (1.54 to 4.31) Non-significant for: • Aspirin vs. placebo (PW 0.71, 0.14 to 3.66; NW 0.65, 0.10 to 3.72) • LMWH vs. placebo (PW not available; NW 1.58, 0.21 to 11.17) • LMWH + aspirin vs. placebo (PW not available; NW 0.80, 0.10 to 5.86) • UFH + aspirin vs. placebo (PW not available; NW 1.70, 0.23 to 10.38) • LMWH + aspirin vs. aspirin (PW 1.33, 0.27 to 4.69; NW 1.18, 0.44 to 3.08) • LMWH + aspirin vs. LMWH (PW not available; NW 0.49, 0.13 to 1.68) • UFH + aspirin vs. LMWH (PW not available; NW 1.04, 0.40 to 2.82) • UFH + aspirin vs. LMWH + aspirin (PW 2.00, 0.62 to 6.47; NW 2.17, 0.87 to 5.77) <u>Women without or without thrombophilia</u> Significant for LMWH vs. aspirin only: • Pair-wise OR 2.07 (95% CI 1.14 to 3.76), Network OR 2.11 (95% CI 1.10 to 3.81) Non-significant for (pair-wise [PW], network [NW]): • Aspirin vs. placebo (PW 0.82, 0.48 to 1.39; NW 0.77, 0.36 to 1.62) • LMWH vs. placebo (PW 1.04, 0.70 to 1.55; NW 1.35, 0.81 to 3.13) • LMWH + aspirin vs. placebo (PW 1.86, 0.68 to 5.06; NW 1.59, 0.81 to 3.13) • LMWH + aspirin vs. aspirin (PW 1.76, 0.87 to 3.56; NW 1.79, 0.93 to 3.54) • LMWH + aspirin vs. LMWH (PW 0.89, 0.47 to 1.67; NW 0.84, 0.43 to 1.81) (Network meta-analysis excluded one trial in women with <2 pregnancy loss)
Comments	Prerequisite to trial inclusion was prior pregnancy loss and main outcome was on improving live birth rate; not directly applicable to asymptomatic screen-detected women and doesn't cover effect on other outcomes. Trials in APS can't tell whether people met diagnostic criteria. Analysis in hereditary thrombophilia can't be included because of apparent mixed population of women with an without thrombophilia Safety outcomes not uniformly reported.

	Small sample size of trials may have led` to insufficient power. Significant between-trial heterogeneity. Likely variable dosing and gestation at onset of treatment. Main risk of bias in included trials was lack of blinding.

Appendix number	5
Relevant criteria	10
Publication details	Areia AL, Fonseca E, Areia M, et al. Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. Archives of Gynecology and Obstetrics. 2016;293(1):81-6.[26]
Study details	Systematic review and meta-analysis
Study objectives	To determine if LMWH plus aspirin improves live birth rate compared with aspirin alone in pregnant women with hereditary thrombophilia.
Inclusions	RCTs in pregnant women with hereditary thrombophilia (FVL, MTHFR, PT or AT deficiency or protein C or S deficiency) comparing LMWH plus aspirin with aspirin alone and examining the effect on live birth rate. Search date June 2014, PubMed, Cochrane Controlled Trials Register, EMBASE, Scopus, ISI Web of Knowledge.
Exclusions	Studies in women with APS, not looking at the study interventions of interest, or non-randomised studies
Population	4 RCTs, n=222. One study (de Vries) including women with prior pre-eclampsia, the others in women with recurrent pregnancy loss. Two studies using dalteparin (5000 IU), enoxaparin (40mg) and nadroparin (2850 IU). Intervention started <14 weeks in all studies , with earliest at 5-6 and latest at 12-13
Intervention	LMWH plus aspirin
Comparator	Aspirin alone
Results/outcomes	Primary outcome live birth rate: • OR 1.70 (95% CI 0.72 to 4.00), I^2 0%. Secondary outcomes: • First trimester miscarriage OR 0.69 (95% CI 0.22 to 2.16), I^2 10% • Preterm birth OR 0.99 (95% CI 0.4 to 2.08), I^2 0%

	• Pre-eclampsia OR 1.49 (95% CI 0.63 to 3.5), I^2 0% • SGA baby OR 2.08 (95% CI 0.96 to 4.47), I^2 0%
Comments	Applicability issue due to inclusion of individuals with additional risk factors. Included trials had low risk of bias for randomisation or allocation concealment but were not blinded. No trial heterogeneity for main outcome but variable thrombophilia variants, LMWH drug and dose and gestation at treatment onset. Safety outcomes not uniformly reported. Limited comparison of one intervention and control and small aggregate sample size despite four trials.

Appendix number	6
Relevant criteria	10
Publication details	Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. 2016;127(13):1650-5.[27]
Study details	Systematic review and meta-analysis
Study objectives	To determine whether the use of prophylactic-dose LMWH (with or without aspirin) reduces the risk of pregnancy loss when compared with no LMWH (with or without aspirin) in women with hereditary thrombophilia and prior late or recurrent loss.
Inclusions	RCTs in pregnant women with hereditary thrombophilia and prior late (≥10 weeks) or recurrent early (≥ 2 losses at <10 weeks) pregnancy loss, randomly allocated to prophylactic-dose LMWH with or without aspirin vs. no LMWH with or without aspirin, and looking at the primary outcome of live birth rate. Search date September 2015, various including Medline, EMBASE, Cochrane Database of Systematic Reviews and Controlled Trials Register, Database of Abstracts of Reviews of Effects, Cochrane Methodology, Health Technology Assessment, and National Health Service Economic Evaluation.
Exclusions	Studies in women with APS, not looking at the study interventions of interest, or non-randomised studies
Population	8 RCTs, n=483. 4 trials included LMWH + aspirin, and 5 trials LMWH only. The control groups

	included 4 trials with aspirin and 5 without. One of the trials of LMWH vs. no LMWH allowed aspirin use in either arm. Pregnancy loss definitions varied.
Intervention	LMWH (+/- aspirin)
Comparator	No LMWH (+/- aspirin)
Results/outcomes	Primary outcome live birth rate: • All trials: 84.5% intervention vs. 64.9% control; RR 0.81 (95% CI 0.55 to 1.19), I^2 91.9% • Multicentre: 83.5% intervention vs. 82.4% control; RR 1.04 (95% CI 0.93 to 1.16), I^2 12.9% Secondary outcomes: • Prior late loss, all trials: 84.2% vs. 59.0%; RR 0.81 (95% CI 0.38 to 1.72), I^2 95.3% • Prior late loss, multicentre trials: 81.9% vs. 90.8%; RR 1.12 (95% CI 0.97 to 1.30), I^2 0% • Prior recurrent early loss: 86.5% vs. 86.2%; RR 0.97 (95% CI 0.80 to 1.19), I^2 n/a
Comments	Applicability issue due to inclusion of women with prior recurrent or late pregnancy loss. Included trials had low risk of bias for randomisation, allocation concealment and selective reporting, but were not blinded. Low heterogeneity when analysing only multicentre trials, but variable thrombophilia variants, LMWH drug and dose, gestation at treatment onset and definition of pregnancy loss. Safety outcomes not uniformly reported. Difficult to isolate the effect of LMWH alone vs. with aspirin. Limited comparison of one intervention and control and small aggregate sample size despite large number of trials.

Appendix ii

Natural history assessment of four post-2010 cohorts investigating links between thrombophilia variants and adverse pregnancy outcomes

Summary table of the four cohorts

Study	Design/Setting	Exposed population	Comparison population	Primary outcome	Association (95% CI)
Rodger et al. 2014[6]	Prospective cohort Canada, 2 centres, 2002-10	N=507 with FVL and/or PT mutation	N=6836 without thrombophilia	Composite of pre-eclampsia, pregnancy loss SGA baby (<10%), placental abruption	aRR 1.07 (0.83 to 1.37) Secondary individual outcomes ns.
Silver et al. 2010[8]	Prospective cohort US, 13 centres, 2000-01	N=157 with PT mutation	N=4010 without thrombophilia	Preeclampsia Pregnancy loss SGA baby (<10%) Placental abruption (no primary reported)	aOR 1.30 (0.56 to 3.02) aOR 0.98 (0.49 to 1.95) aOR 1.34 (0.80 to 2.25) aOR 2.23 (0.52 to 9.58)
Said et al. 2010[7]	Prospective cohort Australia, 2 centres, 2000-03	Unclear: total cohort 1707 Apparently total 2491 hetero- or homozygous for FVL, PT, MTHFR (C677T or A1298C), or thrombomodulin	Unclear: total cohort 1707 Unclear whether comparison to no mutation or any other mutation	Composite of severe pre-eclampsia, SGA baby (<5%), placental abruption, stillbirth or neonatal death	PT heterozygous: aOR 3.58 (1.20 to 10.61) MTHFR A1298C homozygous: aOR 0.26 (0.08 to 0.86) All other variants ns. Isolated significant findings for secondary individual outcomes.
Nili et al. 2013[5]	Retrospective cohort Canada, Nova Scotia Atlee Perinatal Database (NSAPD), 1988-2008	N=58 with aPL (aCL, anti-β2GPI or LA)	N=210,987 without aPL	Pregnancy-induced hypertension Preterm birth VTE (no primary reported)	aOR 2.2 (1.1 to 4.3) aOR 2.2 (1.1 to 4.3) OR 37.6 (6.13 to 130.6) - ns adjusted (not reported)

Full extraction of each study

Publication details	Rodger MA, Walker MC, Smith GN, et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. Journal of Thrombosis and Haemostasis. 2014;12(4):469-78.[6]
Study details	Prospective cohort, Canada (Ottawa and Kingston (OaK) Birth Cohort); 2002 to 2010.
Study objectives	To conduct a large prospective cohort to determine whether FVL and/or prothrombin gene mutation were associated with a composite outcome of placenta-mediated pregnancy complications (pre-eclampsia, SGA baby, pregnancy loss, placental abruption). Secondary objectives were to analyse the association between the individual mutations and the individual outcomes.
Inclusions	Pregnant women attending The Ottawa Clinic or Kingston General Hospital <20 weeks gestation
Exclusions	>20 weeks pregnancy at recruitment, >1 fetus or non-viable fetus.
Population	N=7343 with complete exposure and outcome data available (of 8027 eligible). Mean age 30.4 years, 50.4% nulliparous, prior pre-eclampsia 2.9%, prior SGA baby 0.76%, prior placental abruption 0.8%, prior stillbirth 1.12%, prior RPL (>2) 6.14%.
Exposure group	N=507 (6.9%) with FVL and/or prothrombin mutation: 357 (4.9%) with FVL, 162 (2.2%) with prothrombin mutation, 12 (0.2%) double heterozygotes for both, 8 (0.11%) FVL homozygotes, 3 (0.04%) prothrombin homozygotes.
Comparator	N=6836 without thrombophilia.
Results/outcomes	<u>Composite primary outcome</u> • No thrombophilia 768 (11.23%) • FVL/prothrombin: 59 (11.64%) • Heterozygous FVL: 44 (13.06%) • Heterozygous prothrombin: 13 (8.84%) • FVL and/or prothrombin RR 1.04, 95% CI 0.81 to 1.33; multi-adjusted model 1.07, 95% CI 0.83 to 1.37 SGA was the most common specific complication (total 505, 6.95%) followed by pre-eclampsia (229, 3.12%). Pregnancy loss and placental abruption had incidence of <1% each. In secondary analysis, no significant associations found between FVL and/or prothrombin mutation and any specific outcome. Multi-adjusted RR (95% CI): • SGA 1.03 (0.75 to 1.43)

	• Pre-eclampsia 1.14 (0.70 to 1.85) • Placental abruption 0.60 (0.19 to 1.91) • Pregnancy loss 1.02 (0.45 to 2.34) <u>Addition to meta-analysis</u> Also added the results to their previous 2010 meta-analysis[9] including 11 prospective cohorts. No association between prothrombin mutation and pre-eclampsia, SGA baby, pregnancy loss and placental abruption. FVL no association with the exception of pregnancy loss only (RR 1.79, 95% CI 1.06 to 3.03; 7 cohorts, I^2 53%).
Comments	Large, unselected population that should be applicable to the UK (prior pregnancy complications balanced between groups). Sample size calculated *a priori* based on an expected event rate of 17% for the composite outcome and 8% for FVL and prothrombin mutation. Interim sample calculation based on event rate lower than expected. Determined that 7063 participants would have had over 80% power to detect a clinically important odds ratio difference of 1.5. May be underpowered for individual outcomes due to low event rate. Data available for 91% of the potentially eligible sample. Diagnosis of outcomes based on criteria and reviewed by three adjudicators which should reduce risk of misclassification. Adjudicators also unaware of thrombophilia status. Looks specifically at placenta-mediated complications but not VTE which may have association. Anticoagulant use was low but was slightly higher in the thrombophilia group (3.16% vs. 0.66%). No other hereditary thrombophilia variants tested for – antithrombin, protein C or S deficiency – and homozygotes or double heterozygotes not assessed. The methods of the additional meta-analysis aren't completely clear. The study describes finding one additional post-2010 study (not specified), but have added two additional studies not included in their previous review – their current study and one other.

Publication details	Silver RM, Zhao Y, Spong CY, et al. Prothrombin gene G20210A mutation and obstetric complications. Obstetrics and Gynecology. 2010;115(1):14-20.[8]

Study details	Prospective cohort, 13 clinical centres in the US (the Eunice Kennedy Shriver National Institute of Child Health and Human Development); 2000-01.
Study objectives	To estimate whether maternal carriage of the prothrombin gene G20210A mutation is associated with pregnancy loss, preeclampsia, placental abruption, or SGA baby in a low-risk, prospective cohort. Secondary analysis of 2005 study which had assessed the links with FVL.
Inclusions	Women with uncomplicated singleton pregnancies at ≤14 weeks gestation or less
Exclusions	Multiple gestation, current or planned anticoagulation therapy, FVL, antiphospholipid syndrome, previous VTE, fetal death, planned pregnancy termination.
Population	N=4167 with complete exposure and outcome data available (of 5188 eligible). Mean age 25 years, 31% nulliparous, prior SGA baby 1%, prior pregnancy loss 23%.
Exposure group	N=157 (3.8%) with prothrombin mutation. 156 heterozygotes, 1 homozygous.
Comparator	N=4010 without thrombophilia
Results/outcomes	No significant association between prothrombin mutation and any outcome (adjusted for maternal age, race, parity, prior pregnancy loss, prior SGA baby, and family history of VTE): • Pregnancy loss: carrier 9 (5.7%) vs. non-carrier 238 (6.0%); OR 0.98, 95% CI 0.49 to 1.95 • Pre-eclampsia: 6 (3.8%) vs. 123 (3.1%); OR 1.30, 95% CI 0.56 to 3.02 • SGA 5%: 8 (5.4%) vs. 151 (4.0%); OR 1.39, 95% CI 0.67 to 2.89 • SGA 10%: 17 (11.6%) vs. 338 (9.0%); OR 1.34, 95% CI 0.80 to 2.25 • Placental Abruption: 2 (1.27%) vs. 24 (0.6%); OR 2.23, 95% CI 0.52 to 9.58 • Preterm delivery: 23 (15.3%) vs. 458 (12.1%); OR 1.39, 95% CI 0.87 to 2.21 • Oligohydramnios: 8 (5.1%) vs. 177 (4.4%); OR 1.18, 95% CI 0.57 to 2.44 3 postpartum VTE, all in non-thrombophilia group
Comments	Large, unselected population that should be applicable to the UK (prior pregnancy complications balanced between groups). However, analysis of 2001/02 population may reduce applicability to current population. Diagnosis of outcomes based on criteria. Assessors unaware of thrombophilia

	status. Data unavailable for 20% of the potentially eligible sample. Exclusion of women who were considered candidates for thromboprophylaxis may have excluded higher risk women. >95% power to detect differences in common outcomes (pregnancy loss rate 6% and preterm delivery rate 12%), but may have been underpowered to detect small differences in the rarer outcomes. Only FVL, prothrombin mutation and APS tested – women could have other thrombophilia variants

Publication details	Said JM, Higgins JR, Moses EK, et al. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. Obstetrics and Gynecology. 2010;115(1):5-13.[7]
Study details	Prospective cohort, Australia (two tertiary centres - The Royal Women's Hospital and the Mercy Hospital for Women, Melbourne), 2000 to 2003.
Study objectives	To estimate prospectively the risk of adverse pregnancy outcomes in asymptomatic carriers of inherited thrombophilia polymorphisms including factor V Leiden, prothrombin mutation, MTHFR mutations C677T and A1298C, and thrombomodulin C1418T mutation (latter not a focus of this review).
Inclusions	Gestation <22 weeks, nulliparous (no prior pregnancy exceeding 20 weeks), no personal or family history of VTE or hereditary or acquired thrombophilia.
Exclusions	Multiple pregnancy, major congenital anomalies, essential hypertension, recurrent pregnancy loss (≥3), underlying medical problems associated with a risk of adverse pregnancy outcomes (e.g. systemic lupus erythematosus, renal disease, pre-existing diabetes), and substance use (other than nicotine).
Population	N=1707 with full exposure and outcome data available (of 2034 recruited). Age 29 years, BMI 25.
Exposure group	Number with thrombophilia unclear, apparently 2491 with a mutation (exceeds cohort size) • FVL homozygote 1 (0.06%), heterozygote 92 (5.39) • Prothrombin heterozygous 41 (2.38) • MTHFR C677T homozygous 199 (11.66), heterozygous 742 (43.47) • MTHFR A1298C homozygous 166 (9.72), heterozygous 712 (41.71) • Thrombomodulin homozygous 60 (3.51), heterozygous 478 (28.00) Unclear what proportion may have been compound heterozygotes.

Comparator	As above, number without thrombophilia unclear and not specified
Results/outcomes	Primary outcome: composite of severe preeclampsia, placental abruption (9, 0.5%), SGA baby <5%, stillbirth and neonatal death. Experienced by 136 of all women (8%): severe preeclampsia (32, 1.9%), placental abruption (9, 0.5%), SGA <5% (91, 5.3%), stillbirth (6, 0.4%) and neonatal death (4, 0.2%) (6 women experienced more than one complication). Significant association (adjusted for ethnicity and smoking status) for: • Prothrombin heterozygous: OR 3.58, 95% CI 1.20 to 10.61, p=0.02 • MTHFR A1298C homozygous: OR 0.26, 95% CI 0.08 to 0.86,p=0.03 Non-significant for rest: • FVL homozygote: 1.24 (0.49 to 3.15) • MTHFR C677T heterozygous: 1.08 (0.65 to 1.77) • MTHFR C677T homozygous: 0.97 (0.44 to 2.13) • MTHFR A1298C heterozygous: 0.73 (0.44 to 1.19) • Thrombomodulin heterozygous: 1.28 (0.77 to 2.12) • Thrombomodulin homozygous: 1.24 (0.36 to 4.35) Secondary outcomes: individual outcomes of the primary composite, plus less severe complications of preeclampsia and SGA baby <10%. Isolated significant findings for: • MTHFR A1298C homozygous: SGA baby <5% (0.35, 0.12 to 0.97) and SGA baby <10% (0.42, 0.21 to 0.83) • MTHFR A1298C heterozygous: SGA baby <10% (0.65, 0.47 to 0.90) • Prothrombin mutation heterozygous: placental abruption (12.15, 2.45 to 60.39) • FVL: stillbirth (8.85, 1.60 to 48.92) All others non-significant. Secondary composite of less severe outcomes: mild preeclampsia, gestational hypertension, SGA between the 5th and 10th centiles, prematurity, 5-minute Apgar score <7, and admission to the neonatal nursery for any reason (not defined – reports admission to NICU after discharge not included): • Non-significant for any thrombophilia

Comments	Large, unselected population that should be applicable to the UK. However, quality of reporting is quite low. Total numbers in exposure and comparator groups for each analysis is unclear and prevalence of thrombophilia variants seems very high. Unclear who groups are exposed to for the primary analysis – all others (including other thrombophilia) or non-thrombophilia only Also analysis of 2000/03 population may reduce applicability to current population. Diagnosis of outcomes based on criteria. Assessors unaware of thrombophilia status. Sufficiently powered for the composite outcome: sample size of 2000 calculated to give 80% power to detect OR 2.0 difference in the frequency of severe pregnancy complications with thrombophilia. However, likely underpowered for the individual outcomes, particularly rarer ones. Predominantly representative of severe outcomes. VTE not assessed. 279 of initial 2034 excluded due to various causes, including loss to follow-up (162), miscarriage, congenital abnormalities and terminations. Some of those excluded with these causes may have had thrombophilia, though prevalence is reported to be similar among those lost to follow-up. Doesn't examine antithrombin, protein C or S deficiencies.

Publication details	Nili F, McLeod L, O'Connell C, et al. Outcomes of pregnancies in women with suspected antiphospholipid syndrome. Journal of Neonatal-Perinatal Medicine. 2013;6(3):225-30.[5]
Study details	Retrospective cohort, Canada (Nova Scotia Atlee Perinatal Database, NSAPD); 1988 to 2008.
Study objectives	To evaluate the extent of maternal and neonatal morbidity in pregnancies suspected to have primary antiphospholipid syndrome (APS).
Inclusions	Women of >20 weeks gestation positive for antiphospholipid antibodies (aPL) – anticardiolipin antibodies (aCL), anti-β2 glycoprotein I antibodies (anti-β2GPI) or lupus anticoagulant (LA). Comparison group – all other pregnant women without positive aPL or other rheumatologic disease who delivered between January 1, 1988 and December 31, 2008.
Exclusions	Women with rheumatologic disease as coded in the NSAPD database including SLE, rheumatoid arthritis, Sjogren's syndrome, ankylosing spondylitis, and scleroderma
Population	N=211,034

Exposure group	N=58 (52 with aCL and 6 with LA)
Comparator	N=210,987 without aPL

Results/outcomes	Primary outcome not specified.
	
	Compared to controls women with aPLs were significantly:
	• Older (31 vs. 28)
	• Had more prior pregnancies (3 vs. 2)
	• Longer hospital stay (4 vs. 3.1 days)
	• Babies smaller (2968.2 vs. 3431.5 grams), preterm (36.9 vs. 39.1 weeks), lower Apgar (8 vs. 9 at 1min and 9 vs. 9 at 5mins)
	• Greater proportion women with history of:
	  ○ fertility problems ratio (OR, 6.7, 95% CI 2.1 to 19.2)
	  ○ prior pregnancy loss (OR 9.2, CI 4.8 to 12.3)
	  ○ fetal or neonatal death (OR 8.2, CI 2.6 to 21.6)
	  ○ low birthweight baby (OR 5.5, CI 2.6 to 11.3)
	  ○ VTE (OR 57.2, CI 14.2 to 191.5)
	  ○ pregnancy-induced hypertension (OR 4.3, CI 2.0 to 8.7)
	• Greater proportion with asthma (2.7, 1.0 to 5.9), depression (11.2, 4.0 to 26.3) and other diseases (glomerulomephritis, thrombocytopenia, endocrine or heart disease: 7.2, 3.6 to 14.1)
	
	In current pregnancy the following were more common in women with aPL:
	• VTE: OR 37.6 (95% CI 6.13 to 130.6) (n not reported)
	• Pre-existing or pregnancy-induced hypertension: OR 3.2 (95% CI 1.7 to 6.2) (25.9% vs. 9.7%)
	• Also UTI, group B infection, induction of labour and caesarean rate
	
	Multi-adjustment (for age, prior pregnancies, prenatal corticosteroids, low dose aspirin, maternal congenital heart disease, asthma, endocrine diseases, chronic glomerulonephritis, chronic hypertension, depression, pregnancy-induced hypertenion, urinary tract infection, colonization with streptococcus group B, gestational age at birth, birth weight, and neonatal anomalies) found only the following outcomes were significantly associated with aPLs:
	• Pregnancy-induced hypertension: OR 2.2 (95% CI 1.1 to 4.3)

	• Maternal urinary tract infection: OR 2.3 (95% CI 1.1 to 4.7) • Gestational age ≤37 weeks: OR 2.2 (95% CI 1.1 to 4.3) • Maternal congenital heart disease: OR 26.7 (95% CI 6.9 to 103.9) Reported no difference in rates of severe pregnancy hypertension, oligohydramnios, polyhydramnios, prelabor rupture of membranes, premature rupture of membranes, rupture of membranes >24 hours, meconium stained amniotic fluid, chorioamnionitis, placenta previa or abruption, haemorrhage (antepartum, intrapartum, postpartum), gestational or pre-gestational diabetes and pyelonephritis.
Comments	Limited by retrospective design. Large, unselected population that should be applicable to the UK but may be limited by the fact that during the study period there were no specific guidelines for measuring aPLs and no systematic coding for APS in the database. Testing and treatment at doctor's discretion (19% of women received anticoagulants, 29.3% aspirin and 15.5% corticosteroid). Criteria for diagnosis likely differed between doctors, so unclear who met current diagnostic criteria for APS. Women not tested prior to 20 weeks gestation. No primary pregnancy outcome specified and likely underpowered to detect differences. Very wide CIs.

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