UK National Screening Committee

SCREENING FOR THROMBOPHILIA ANTENATALLY, IN NEONATES AND IN THE GENERAL ADULT POPULATION

An evidence map to outline the volume and type of evidence related to screening for thrombophilia for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Summary

This document discusses the findings of the evidence map on screening for thrombophilia.

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, no further work on screening for thrombophilia should be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to screening for thrombophilia in 3-years' time.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for thrombophilia antenatally, in neonates and in the general adult population is a topic currently due for an external review update.

Thrombophilia describes a number of variants that increase an individual's risk of thrombosis; the formation of a blood clot obstructing the flow of blood within a blood vessel. It can lead to thrombotic events such as deep vein thrombosis, pulmonary embolism or obstetric complications. Thrombophilia can be acquired or inherited. Acquired thrombophilia is associated with pregnancy, disease such as cancer and autoimmune disease and exposure to some medications such as oral contraception. Inherited thrombophilia is due to inherited deficiencies or abnormalities such as protein deficiencies [1,2].

Previous reviews on screening for thrombophilia

The UK NSC currently recommends against antenatal or newborn screening for thrombophilia or screening for thrombophilia in the general adult population. The Committee based these recommendations on the evidence provided by the 2016 review on universal antenatal screening for thrombophilia carried out by Bazian Ltd [3] and the 2016 review on screening for thrombophilia in neonates and adults carried out by Solutions for Public Health [2].

The 2016 review on universal antenatal screening for thrombophilia [3] considered questions on the risk of adverse pregnancy outcomes for different thrombophilia variants, the performance of universal screening strategies for all pregnant women and the treatment of screen-detected women. The review did not identify any studies on the performance of universal screening tests or studies assessing strategies of universal thrombophilia screening for all pregnant women. The review also did not identify any eligible studies assessing thromboprophylaxis in screen-detected women or women without additional risk factors.

The 2016 review on screening for thrombophilia in neonates and adults [2] considered questions on the performance on screening strategies and the effectiveness of

thromboprophylaxis in screen-detected neonates and adults. The review did not identify any eligible studies to answer these questions.

Current guidance

In guidance published in 2015, the Royal College of Obstetricians and Gynaecologists recommended that all pregnant women should undergo a documented assessment of risk factors for venous thromboembolism with recommendations regarding prophylactic treatment based on the number of risk factors present. The recommendations also include a section on the management of asymptomatic women with inheritable thrombophilia based on an assessment of their level of risk. The guidance states that circumstances in which testing for thrombophilia should be considered include women with a prior venous thromboembolism or women with no personal history or risk factors for venous thromboembolism but a family history of an unprovoked or oestrogen-provoked venous thromboembolism in a first-degree relative aged under 50 years [4].

Guidance from the National Institute of Health and Care Excellence, published in 2012 and partially updated in 2020, covers the diagnosis and management of adults who have developed deep vein thrombosis or pulmonary embolisms. It also covers testing for thrombophilia and other factors that increase the risk of deep vein thrombosis or pulmonary embolisms. Testing is considered for people currently receiving anticoagulation treatment for an unprovoked deep vein thrombosis or pulmonary embolism if there is a plan to stop treatment. Routine testing for people with a family history of thrombophilia is not recommended, nor is testing for hereditary thrombophilia in people who are continuing anticoagulation treatment. Testing for thrombophilia is not recommended for people who have had a provoked deep vein thrombosis or pulmonary embolism, for example following surgery or trauma [5].

There is no UK guidance for neonatal thrombophilia [1].

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on screening for thrombophilia should be commissioned in 2020 and to evaluate the volume and type of evidence on key issues related to screening for thrombophilia antenatally, in neonates and in the general adult population.

The aim was to address the following questions:

1. What is the accuracy of universal screening tests for thrombophilia in the general pregnant population?

2. What is the effectiveness and safety of thromboprophylaxis for preventing venous thromboembolism and adverse pregnancy outcomes in screen-detected women?
3. What is the accuracy of screening tests for detecting thrombophilia in neonates and the general adult population?
4. What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

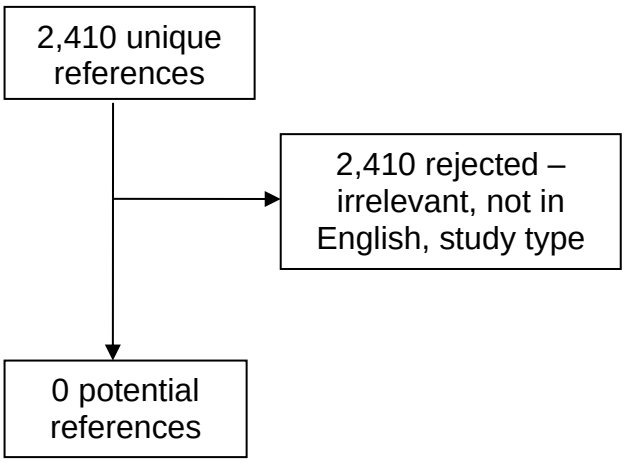
The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on thrombophilia in 2020. The aim of this document is to present the information necessary for the UK NSC to decide this.

Search methods and results

The searches were conducted on 10th July 2020 on 3 databases: Medline, Embase and the Cochrane Library. The search period was restricted to January 2016 – July 2020. The detailed search strategies, including exclusion and inclusion criteria are available in Appendix 1. The search returned a total of 2,410 unique references which were initially sifted by an information scientist for potential relevance. One reviewer assessed 291 titles and abstracts for further appraisal and possible inclusion in the evidence map. No references met the criteria for inclusion in the final evidence map. Studies were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertainty. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

Figure 1: Summary of included and excluded publications



Summary of findings

Question 1: What is the accuracy of universal screening tests for thrombophilia in the general pregnant population?

There are a range of screening tests available for different thrombophilias. These include testing for antithrombin deficiency, protein C or protein S deficiencies, Factor V Leiden mutation, prothrombin gene mutation (G20210A) and anti-phospholipid antibodies [2]. The population of interest for this question is low risk pregnant women [1].

The search did not identify any studies exploring the performance of such tests in a consecutive or random sample of low risk pregnant women. Instead, the studies returned by the search concerned risk factors for adverse pregnancy outcomes, diagnostic assessment in patients referred for testing and case-control studies. The inclusion and exclusion criteria are summarised in Appendix 1.

The UK NSC's current position is that there is insufficient evidence to determine the accuracy of universal screening tests for thrombophilia in a general pregnant population. No studies were identified that met the inclusion criteria for this question. Therefore, there is insufficient new evidence in this key area to justify commissioning an evidence summary about this question.

Question 2: What is the effectiveness and safety of thromboprophylaxis for preventing venous thromboembolism and adverse pregnancy outcomes in screen-detected women?

The search did not identify any studies exploring the effectiveness and safety of thromboprophylaxis for preventing venous thromboembolism and adverse pregnancy outcomes in screen-detected women or asymptomatic women detected by other means. The studies returned by the search instead mainly concerned the treatment of women with a history of adverse pregnancy outcomes or a past thrombotic event. Other studies detected by the search compared treatment outcomes for patients with different risk levels or described practices in a specific centre or country. The inclusion and exclusion criteria are summarised in Appendix 1.

A few of the studies identified had mixed populations and included some women without a prior history of adverse events who could be considered asymptomatic. For example, a prospective cohort study explored the effectiveness of low molecular weight heparin compared to no treatment on pregnancy outcomes in women regardless of whether they had a history of adverse events. However, the authors stated that a large number of patients in both groups had previous adverse pregnancy outcomes and did not separately report outcomes for any women without such history [6]. In addition, a retrospective study described better perinatal outcomes for women with inherited thrombophilia who were treated with low molecular weight heparin compared to women who were not treated. However, although the authors reported that women had better outcomes if they did not have a history of recurrent pregnancy loss compared to women with a past history of pregnancy loss, this was not a study comparing treatment or no treatment in women without prior pregnancy loss [7].

The UK NSC's current position is that there is insufficient evidence to determine the effectiveness of thromboprophylaxis in screen-detected women. No studies were identified that met the inclusion criteria for this question. Therefore, there is insufficient new evidence in this key area to justify commissioning an evidence summary about this question.

Question 3: What is the accuracy of screening tests for detecting thrombophilia in neonates and the general adult population?

The search did not identify any studies exploring test performance in a consecutive or random sample of a general adult population. Instead, the studies returned by the search were about testing for thrombophilia in patients who had been refereed for testing, who had already experienced a thrombotic event, or were case-control studies. Other studies explored different potential risk factors or biomarkers for thrombotic events.

The search did not identify any studies exploring test performance in a consecutive or random sample of neonates. The few studies on neonates identified by the search were case-control studies.

The inclusion and exclusion criteria are summarised in Appendix 1.

The UK NSC's current position is that there is insufficient evidence to determine the accuracy of universal screening tests for thrombophilia in neonates or a general adult population. No studies were identified that met the inclusion criteria for this question. Therefore, there is insufficient new evidence in this key area to justify commissioning an evidence summary about this question.

Question 4: What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

The search did not identify any studies exploring the effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates or adults. Instead the studies returned by the search concerned the use of thromboprophylaxis to prevent recurrence in adults or neonates who had experienced a thrombotic event, the withdrawal of treatment, the impact of existing treatment on testing for thrombophilia and practices in a centre or country. The inclusion and exclusion criteria are summarised in Appendix 1.

Although no studies met the inclusion criteria, a systematic review was identified that included a section on thromboprophylaxis in asymptomatic antiphospholipid syndrome* carriers with a high-risk antiphospholipid syndrome profile with or without traditional risk factors [8]. It is not clear how these individuals were identified. This review was conducted to inform the development of European recommendations and searched for studies published up to January 2018. However, the included studies were all published prior to 2016 and were therefore not eligible for inclusion in this evidence map.

A Cochrane review searched for studies published up to May 2016 on the use of heparin compared to placebo or no treatment for the management of thrombosis in neonates [9]. This review did not identify any eligible studies.

The UK NSC's current position is that there is insufficient evidence to determine the effectiveness of thromboprophylaxis in screen-detected neonates or adults. No studies were identified that met the inclusion criteria for this question. Therefore, there is insufficient new evidence in this key area to justify commissioning an evidence summary about this question.

* Tests for thrombophilia include testing for antiphospholipid antibodies

Conclusions

There was a lack of studies meeting the inclusion criteria for the key questions. The findings of this evidence map are unlikely to impact on current recommendations on screening for thrombophilia antenatally, in neonates or in the general adult population as no new evidence was identified that would change those conclusions.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to screening for thrombophilia is currently insufficient to justify an update review at this stage and so should be re-considered in 3-years' time.

Appendix 1 — Search strategies for the evidence map

Question 1 – Screening tests in pregnancy

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2016 to 10th July 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	exp Thrombophilia/	25231	1	thrombophilia/ or antiphospholipid syndrome/ or protein c deficiency/ or protein s deficiency/ or blood clotting factor 5 Leiden/	35801
2	thrombophili*.ti,ab,kw.	7737	2	thrombophili*.ti,ab,kw.	14248
3	hypercoagula*.ti,ab,kw.	9602	3	hypercoagula*.ti,ab,kw.	15208
4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1020	4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1492
5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	4047	5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	6611
6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	1205	6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	2104
7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	4410	7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	6393
8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	7959	8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	11304
9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	7872	9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	12276
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	53352	10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	64545
11	exp Pregnancy/ or Pregnant Women/	892897	11	exp pregnancy/ or pregnant woman/ or exp pregnancy complication/	743699
12	Prenatal Care/	27603	12	Prenatal Care/ or prenatal period/	49384
13	Infant, Newborn/	602767	13	newborn/	525516
14	(prenatal or pre-natal or prepart* or pre-part* or antenatal or ante-natal or antepart* or ante-part* or pregna* or maternal or obstetric* or expectant mother* or neonat* or newborn*).ti,ab,kw.	1058924	14	(prenatal or pre-natal or prepart* or pre-part* or antenatal or ante-natal or antepart* or ante-part* or pregna* or maternal or obstetric* or expectant mother* or neonat* or newborn*).ti,ab,kw.	1283626
15	11 or 12 or 13 or 14	1690298	15	11 or 12 or 13 or 14	1687809
16	Mass Screening/	103135	16	screening/ or mass screening/ or screening test/	296302
17	exp Blood Coagulation Tests/	41044	17	blood clotting test/	10263
18	(screen* or detect* or diagnos* or test*).ti,ab,kw.	7145870	18	(screen* or detect* or diagnos* or test*).ti,ab,kw.	9442545

19	exp "Sensitivity and Specificity"/	583079	19	"sensitivity and specificity"/ or predictive value/ or diagnostic accuracy/	646751
20	(predict* or accuracy or sensitiv* or specific*).ti,ab,kw.	5454409	20	(predict* or accuracy or sensitiv* or specific*).ti,ab,kw.	6888330
21	16 or 17 or 18 or 19 or 20	10591521	21	16 or 17 or 18 or 19 or 20	13479964
22	10 and 15 and 21	5133	22	10 and 15 and 21	8144
23	prenatal diagnosis/ or maternal serum screening tests/	37442	23	prenatal diagnosis/ or prenatal screening/	64443
24	Neonatal Screening/	10147	24	newborn screening/	18982
25	23 or 24	47262	25	23 or 24	82544
26	10 and 25	104	26	10 and 25	268
27	22 or 26	5156	27	22 or 26	8199
28	exp animals/ not humans/	4715310	28	(exp animals/ or nonhuman/) not human/	6529108
29	27 not 28	5071	29	27 not 28	8041
30	(case reports or comment or congress or editorial or letter or news or "review").pt. or case report.ti,ab.	6563580	30	(conference* or editorial or letter or note or review).pt. or case report/	11680118
31	29 not 30	2867	31	29 not 30	2809
32	limit 29 to ("systematic review" or "reviews (maximizes specificity)")	128	32	limit 29 to "reviews (maximizes specificity)"	162
33	31 or 32	2949	33	31 or 32	2914
34	limit 33 to (english language and yr="2016 -Current")	571	34	limit 33 to (english language and yr="2016 -Current")	707

Question 2 – Thromboprophylaxis in pregnancy

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2016 to 10th July 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	exp Thrombophilia/	25235	1	thrombophilia/ or antiphospholipid syndrome/ or protein c deficiency/ or protein s deficiency/ or blood clotting factor 5 Leiden/	35761
2	thrombophili*.ti,ab,kw.	7740	2	thrombophili*.ti,ab,kw.	14234
3	hypercoagula*.ti,ab,kw.	9606	3	hypercoagula*.ti,ab,kw.	15208
4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1020	4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1487
5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	4048	5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	6593
6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	1205	6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	2102
7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	4410	7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	6379
8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	7959	8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	11297
9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	7875	9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	12266

10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	53365	10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	64496
11	exp Pregnancy/ or Pregnant Women/	893121	11	exp pregnancy/ or pregnant woman/ or exp pregnancy complication/	743507
12	Prenatal Care/	27617	12	Prenatal Care/ or prenatal period/	49400
13	Infant, Newborn/	602919	13	newborn/	525348
14	(prenatal or pre-natal or prepart* or pre-part* or antenatal or ante-natal or antepart* or ante-part* or pregna* or maternal or obstetric* or expectant mother* or neonat* or newborn*).ti,ab,kw.	1059443	14	(prenatal or pre-natal or prepart* or pre-part* or antenatal or ante-natal or antepart* or ante-part* or pregna* or maternal or obstetric* or expectant mother* or neonat* or newborn*).ti,ab,kw.	1E+06
15	11 or 12 or 13 or 14	1690907	15	11 or 12 or 13 or 14	2E+06
16	exp anticoagulants/	220746	16	exp anticoagulant agent/	655430
17	(heparin* or aspirin or lmwh or enoxaparin or dalteparin).ti,ab,kw.	133885	17	(heparin* or aspirin or lmwh or enoxaparin or dalteparin).ti,ab,kw.	186558
18	(anticoagulat* or anti-coagula*).ti.	11329	18	(anticoagulat* or anti-coagula*).ti.	16719
19	16 or 17 or 18	298948	19	16 or 17 or 18	690576
20	10 and 15 and 19	3348	20	10 and 15 and 19	6778
21	exp animals/ not humans/	4715987	21	limit 20 to "reviews (maximizes specificity)"	115
22	20 not 21	3302	22	randomized controlled trial/	609920
23	(case reports or comment or congress or editorial or letter or news or "review").pt. or case report.ti,ab.	6567095	23	single blind procedure/ or double blind procedure/	211237
24	22 not 23	1529	24	crossover procedure/	63604
25	limit 22 to ("systematic review" or "reviews (maximizes specificity)")	75	25	(random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.	2E+06
26	24 or 25	1588	26	22 or 23 or 24 or 25	2E+06
27	limit 26 to (english language and yr="2016 -Current")	248	27	20 and 26	526
			28	(exp animals/ or nonhuman/) not human/	7E+06
			29	27 not 28	522
			30	21 or 29	584
			31	limit 30 to (english language and yr="2016 -Current")	138

Question 3 – Screening tests general population

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2016 to 10th July 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	exp Thrombophilia/	25235	1	*thrombophilia/ or *antiphospholipid syndrome/ or *protein c deficiency/ or *protein s deficiency/ or *blood clotting factor 5 Leiden/	16553
2	thrombophili*.ti,ab,kw.	7740	2	thrombophili*.ti,ab,kw.	14234
3	hypercoagula*.ti,ab,kw.	9606	3	hypercoagula*.ti,ab,kw.	15208

4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1020	4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1487
5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	4048	5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	6593
6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	1205	6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	2102
7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	4410	7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	6379
8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	7959	8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	11297
9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	7875	9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	12266
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	53365	10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	57168
11	Mass Screening/	103155	11	screening/ or mass screening/ or screening test/	296310
12	screen*.ti.	175793	12	screen*.ti.	229646
13	Diagnosis/ or Early Diagnosis/	43662	13	Diagnosis/ or Early Diagnosis/	1422762
14	exp Blood Coagulation Tests/	41053	14	blood clotting test/	10260
15	(screen* or detect* or diagnos* or test*).ti,ab,kw.	7150159	15	(screen* or detect* or diagnos* or test*).ti,ab,kw.	9446272
16	13 or 14 or 15	7186847	16	13 or 14 or 15	9934353
17	exp "Sensitivity and Specificity"/	583239	17	"sensitivity and specificity"/ or predictive value/ or diagnostic accuracy/	647006
18	(predict* or accuracy or sensitiv* or specific*).ti,ab,kw.	5457925	18	(predict* or accuracy or sensitiv* or specific*).ti,ab,kw.	6889970
19	17 or 18	5656358	19	17 or 18	7068386
20	16 and 19	2253132	20	16 and 19	3097273
21	11 or 12 or 20	2405934	21	11 or 12 or 20	3381506
22	10 and 21	5240	22	10 and 21	8607
23	exp animals/ not humans/	4715987	23	(exp animals/ or nonhuman/) not human/	6531156
24	22 not 23	5101	24	22 not 23	8366
25	(case reports or comment or congress or editorial or letter or news or "review").pt. or case report.ti,ab.	6567095	25	(conference* or editorial or letter or note or review).pt. or case report/	11674942
26	24 not 25	3606	26	24 not 25	3330
27	limit 24 to ("systematic review" or "reviews (maximizes specificity)")	154	27	limit 24 to ("systematic review" or "reviews (maximizes specificity)")	226
28	26 or 27	3696	28	26 or 27	3472
29	limit 28 to (english language and yr="2016 -Current")	847	29	limit 28 to (english language and yr="2016 -Current")	793

Question 4 –Thromboprophylaxis general population

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2016 to 10th July 2020

SEARCH STRATEGIES:

Medline			Embase		
1	exp Thrombophilia/	25235	1	*thrombophilia/ or *antiphospholipid syndrome/ or *protein c deficiency/ or *protein s deficiency/ or *blood clotting factor 5 Leiden/	16553
2	thrombophili*.ti,ab,kw.	7740	2	thrombophili*.ti,ab,kw.	14234
3	hypercoagula*.ti,ab,kw.	9606	3	hypercoagula*.ti,ab,kw.	15208
4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1020	4	((acp or "activated protein c") adj resistan*).ti,ab,kw.	1487
5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	4048	5	(("factor v" or "factor 5") adj leiden).ti,ab,kw.	6593
6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	1205	6	(prothrombin adj (g2021a or g20210a or mutation?)).ti,ab,kw.	2102
7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	4410	7	(("protein c" or "protein s" or antithrombin or anti-thrombin) adj3 deficien*).ti,ab,kw.	6379
8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	7959	8	(mthfr or methylenetetrahydrofolate).ti,ab,kw.	11297
9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	7875	9	(antiphospholipid syndrome or elevated antiphospholipid* or hughes syndrome).ti,ab,kw.	12266
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	53365	10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	57168
11	exp anticoagulants/	220746	11	exp anticoagulant agent/	7E+05
12	(heparin* or aspirin or lmwh or warfarin or enoxaparin or dalteparin or vitamin k antagonist*).ti,ab,kw.	154977	12	(heparin* or aspirin or lmwh or warfarin or enoxaparin or dalteparin or vitamin k antagonist*).ti,ab,kw.	2E+05
13	(oral anticoagula* or oral anti-coagula* or doac* or noac* or rivaroxaban or apixaban or dabigatran or edoxaban).ti,ab,kw.	23216	13	(oral anticoagula* or oral anti-coagula* or doac* or noac* or rivaroxaban or apixaban or dabigatran or edoxaban).ti,ab,kw.	41779
14	(anticoagulat* or anti-coagula*).ti.	11329	14	(anticoagulat* or anti-coagula*).ti.	16719
15	11 or 12 or 13 or 14	308696	15	11 or 12 or 13 or 14	7E+05
16	10 and 15	15211	16	10 and 15	22573
17	limit 16 to ("systematic review" or "reviews (maximizes specificity)")	215	17	limit 16 to "reviews (maximizes specificity)"	266
18	randomized controlled trial.pt.	509327	18	randomized controlled trial/	6E+05
19	controlled clinical trial.pt.	93750	19	single blind procedure/ or double blind procedure/	2E+05
20	randomized.ab.	485410	20	crossover procedure/	63604
21	placebo.ab.	209235	21	(random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.	2E+06
22	clinical trials as topic.sh.	192007	22	18 or 19 or 20 or 21	2E+06
23	randomly.ab.	336668	23	16 and 22	1550
24	trial.ti.	221381	24	(exp animals/ or nonhuman/) not human/	7E+06
25	18 or 19 or 20 or 21 or 22 or 23 or 24	1299605	25	23 not 24	1493
26	16 and 25	966	26	17 or 25	1654
27	exp animals/ not humans/	4715987	27	limit 26 to (english language and yr="2016 -Current")	425
28	26 not 27	929			
29	17 or 28	1071			
30	limit 29 to (english language and yr="2016 -Current")	179			

For all 4 questions

Cochrane	
#1	MeSH descriptor: [Thrombophilia] explode all trees
#2	(thrombophilia* or hypercoagulat*):ti,ab,kw
#3	(((acp or "activated protein c") NEXT resistan*)):ti,ab,kw
#4	((("factor v" or "factor 5") NEXT leiden)):ti,ab,kw
#5	((prothrombin NEXT (g2021a or g20210a or mutation*))):ti,ab,kw
#6	((("protein c" or "protein s" or antithrombin or anti-thrombin) NEAR/3 deficien*)):ti,ab,kw
#7	(mthfr or methylenetetrahydrofolate):ti,ab,kw
#8	("antiphospholipid syndrome" or "elevated antiphospholipid*" or "hughes syndrome"):ti,ab,kw
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Results by database

Medline	**1,845**
Embase	**2,063**
Cochrane Library	**363**
Total	**4,271**

After the exclusion of duplicates, 2,410 references remained.

Inclusions and exclusions

Publications not in the English language, case reports, conference abstracts, trial protocols and comment/editorials/letters were excluded.

Eligibility for inclusion in the map

Question 1

- population: low risk pregnant women (without indications such as venous thromboembolism themselves or Familial Hypercholesterolemia or venous thromboembolism in a relative <50)
- index test: different panels of screening tests (for example, TREATS modelled F factor V Leiden, prothrombin G20210A, antithrombin, protein C and protein S deficiencies, lupus anticoagulants and anticardiolipin antibodies); tests specifically for antiphospholipid syndrome (for example, lupus anticoagulant and anticardiolipin antibodies)
- comparator: any or none
- reference standard: detection of women with confirmed thrombophilia; or detection of those who experience venous thromboembolism or adverse pregnancy
- outcomes: sensitivity; specificity; false positive rate; false negative rate; positive predictive value; negative predictive value
- study design: prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and the reference standard, or where participants are randomised to different index tests but all receive the reference standard, and assessment in a cross-sectional manner.

Exclusion criteria:

- case-control studies and studies with longitudinal assessment of the reference standard

Question 2

- population: screen-detected pregnant women (with or without additional risk factors), or asymptomatic women detected by other means
- intervention: aspirin; low-molecular-weight heparin; unfractionated heparin; combination
- comparator: placebo; alternative treatment
- outcomes: venous thromboembolism (deep vein thrombosis/ pulmonary embolism); miscarriage; stillbirth; pre-eclampsia; intrauterine growth restriction; placental-abruption; postpartum-haemorrhage
- study design: randomised controlled trials, cohort studies and systematic reviews of the above

Question 3

- population: neonates (excluding neonates with purpura fulminans); adults (excluding a risk group such as people taking the oral contraceptive pill, hormone replacement therapy, patient following major orthopaedic surgery and pregnant women)
- index test: tests for thrombophilia such as: antithrombin deficiency; protein C deficiencies; free protein S deficiencies; factor V Leiden mutation; prothrombin gene mutation (G-20210-A); activated protein C (APC) Resistance Assay; methylenetetrahydrofolate reductase (MTHFR) mutation; antiphospholipid antibodies (aPL) (anticardolipin antibodies (aCL), lupus anticoagulant (LA), anti-beta2-glycoprotein-1 (anti-B2GP1))
- comparator: open
- reference standard: as used by the study
- outcomes: sensitivity; specificity; false positive rate; false negative rate; positive predictive value; negative predictive value
- study design: prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and the reference standard, or where participants are randomised to different index tests but all receive the reference standard, and assessment in a cross-sectional manner.

Exclusion criteria:

- case-control studies and studies with longitudinal assessment of the reference standard

Question 4

- population: neonates (excluding neonates with purpura fulminans); adults (excluding a risk group such as people taking the oral contraceptive pill, hormone replacement therapy, patient following major orthopaedic surgery and pregnant women)
- intervention: anticoagulation management comprises any prescription of anticoagulants
- comparator: neonates or adults with thrombosis who are not screened, and subjected to anticoagulation management; N/A if the study is observational
- outcomes: thromboembolic events (including fatal events) – venous events for population with venous thrombosis including deep vein thrombosis, pulmonary embolism, venous stroke, arterial events for population with arterial thrombosis including arterial stroke and myocardial infarction; mortality; adverse effects of anticoagulation treatment (for example haemorrhage); anticoagulation management measures, including whether or not an anticoagulant is prescribed, frequency of International Normalised Ratio (INR) testing, INR target, duration of anticoagulant prescription, duration of follow-up of patient
- study design: randomised controlled trials, cohort studies and systematic reviews of the above

Appendix 2 – Abstract reporting tables

Question 1 - What is the accuracy of universal screening tests for thrombophilia in the general pregnant population?

No eligible studies identified.

Question 2 - What is the effectiveness and safety of thromboprophylaxis for preventing venous thromboembolism and adverse pregnancy outcomes in screen-detected women?

No eligible studies identified.

Question 3 - What is the accuracy of screening tests for detecting thrombophilia in neonates and the general adult population?

No eligible studies identified.

Question 4 - What is the reported effectiveness of thromboprophylaxis for preventing adverse outcomes in screen-detected neonates and adults?

No eligible studies identified.

References

Introduction

1. UK National Screening Committee. Commissioning document: screening for thrombophilia antenatally, in neonates and in the general adult population – evidence map. June 2020
2. Solutions for Public Health. Neonatal and general adult populations screening for thrombophilia. External review against programme appraisal criteria for the UK National Screening Committee UK NSC). December 2016
3. Bazian Ltd. Antenatal screening for thrombophilia. External review against programme appraisal criteria for the UK National Screening Committee UK NSC). August 2016
4. Royal College of Obstetricians & Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and puerperium. Green-top Guideline No. 37a, April 2015
5. National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NG158, March 2020

Question 1: Screening tests in pregnancy

No studies included.

Question 2: Thromboprophylaxis in pregnancy for screen-detected women

6. Dugalic S, Petronijevic M, Stefanovic A, Stefanovic K, Petronijevic SV, Stanisavljevic D, et al. Comparison of 2 approaches in management of pregnant women with inherited thrombophilias: Prospective analytical cohort study. Medicine. 2019;98(34):e16883
7. Sokol V, Ivanisevic M, Herman M, Delmis J. The Role of Low Molecular Weight Heparin in Women with Hereditary Thrombophilia for Good Perinatal Outcome. Acta Clinica Croatica. 2016, 55(2): 309-15

Question 3: Screening tests in neonates and the general adult population

No studies included.

Question 4: Thromboprophylaxis for screen-detected neonates and adults

8. Tektonidou MG, Andreoli L, Limper M, Tincani A, Ward MM. Management of thrombotic and obstetric antiphospholipid syndrome: a systematic literature

review informing the EULAR recommendations for the management of antiphospholipid syndrome in adults. RMD Open. 2019, 5(1): e000924
9. Romantsik O, Bruschettini M, Zappettini S, Ramenghi LA, Calevo MG. Heparin for the treatment of thrombosis in neonates. Cochrane Database of Systematic Reviews. 2016, 11:CD012185