National Institute for Health and Care Excellence

Draft for consultation

Antenatal care

[N] Risk factors for venous thromboembolism in pregnancy

NICE guideline tbc

Evidence reviews underpinning recommendations 1.2.16 and 1.2.17

February 2021

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Risk factors for venous thromboembolism in pregnancy

Review question

What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Introduction

Venous thromboembolism (VTE) is an important cause of maternal death. For this reason it is important to be able to assess the level of individual risk in pregnant women in order to plan appropriate prevention strategies. The NICE guideline on venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism covers the risk assessment for VTE in pregnant women who are admitted to hospital but does not cover pregnant women in other circumstances The aim of this evidence review is to identify independent risk factors for VTE in pregnant women.

Summary of the protocol

Please see Table 1 for a summary of the Population, Risk factor and Outcome (PRO) characteristics of this review.

Table 1: Summary of the protocol (PRO table)

Population	All pregnant women who are not receiving VTE thromboprophylaxis
Risk factors	Maternal and/or pregnancy-related risk factors associated with the development of venous thromboembolism during pregnancy
Outcomes	Venous thromboembolism during pregnancy

VTE: venous thromboembolism

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Fourteen studies were included in this review. These included 10 population-based cohort studies (Hansen 2017, Jensen 2013, Kane 2013, Lindqvist 1999, Rova 2012, Scheres 2020, Sultan 2013, Sultan 2013a, Virkus 2014, Wang 2019) and 4 population-based nested case-control studies (Galanaud 2010, Larsen 2005, Larsen 2007, Simpson 2001).

Thirteen studies included participants retrospectively from birth or pregnancy records in hospital registers; 1 study (Galanaud 2010) recruited primigravidae women prospectively from an ongoing cohort of women who were regularly followed-up by a network of gynaecologists and obstetricians.

Twelve of the studies examined the association between VTE in pregnancy and risk factors in women who developed VTE compared with women who did not develop VTE during pregnancy (Galanaud 2010, Jensen 2013, Kane 2013, Larsen 2005, Larsen 2007, Lindqvist 1999, Scheres 2020, Simpson 2001, Sultan 2013, Sultan 2013a, Virkus 2014 and Wang 2019). One study examined the association between in-vitro fertilization (IVF) with or without Ovarian hyperstimulation syndrome (OHSS) and VTE during pregnancy by comparing women who conceived by IVF and women who conceived without IVF (Rova 2012). One study compared the association between inflammatory bowel diseases (IBD) with VTE in pregnancy in women with IBD compared with women without IBD (Hansen 2017).

The relevant risk factors for VTE reported in the reviewed studies include: acute respiratory tract infection; maternal age; antenatal haemorrhage; blood group; BMI; cancer (unspecified); deprivation; gestational diabetes; gestational hypertension; history of blood transfusion; history of VTE; hospitalisation; hyperemesis; infection (unspecified); IBD; IVF; medications; miscarriage; multiple pregnancy; parity; pre-eclampsia; pre-existing diabetes (unspecified); pre-existing hypertension; smoking; stroke; thrombophilia (unspecified); F2 20210 A mother (thrombophilia); F12 46T mother (thrombophilia); PROCR 6936G mother (thrombophilia); urinary tract infection; varicose vein; vascular disease; and year of delivery.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

1 Summary of clinical studies included in the evidence review

2 Summaries of the studies that were included in this review are presented in Table 2.

3 **Table 2: Summary of included studies**

Study **Study design** **Country** **Size of cohort**	**Cases** **Number of participants**	**Controls** **Number of participants**	**Potential risk factors examined**	**Covariables adjusted for**
Galanaud 2010 Population-based nested case-control study France N=5,370 women	N=66 women with DVT (46 DVT events in pregnancy; 20 DVT cases in postpartum) Women with first symptomatic VTE (DVT or PE)	N=5,304 women free of VTE Women without previous VTE	• Age (Maternal) • BMI • Conceptus weight • F5 1691A mother • F2 20210A mother • F12 46T mother • PROCR 6936G mother • PROCR 6936G father • Miscarriage	• Age (Maternal) • BMI • Conceptus weight • Miscarriage • F5 1691A mother • F2 20210A mother • F12 46T mother • PROCR 6936G mother • PROCR 6936G father
Hansen 2017 Population-based retrospective cohort study Denmark N=1,046,754 women	N=11,978 pregnancies in women with IBD 36 VTE events in pregnancy	N=1,966,289 pregnancies in women without IBD 3429 VTE events in pregnancy	• IBD	• Age (Maternal) • BMI (Maternal pre-pregnancy) • Smoking
Jensen 2013	N= 337 pregnancies with VTE	N=299,473 pregnancies without VTE	<u>Non-pharmacological risk factors for VTE</u> • Age (Maternal)	<u>Adjusted for in non-pharmacological risk factor analysis</u> • Age (Maternal)

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
Population-based retrospective cohort study Denmark N= 299,810 pregnancies			• BMI (pre-pregnancy) • Gestational diabetes • Gestational hypertension • Hyperemesis • Parity • Pre-eclampsia • Previous VTE • Smoking • Stroke • Thrombophilia • Vascular disease <u>Pharmacological</u> • A02BC: Proton pump inhibitors • A07EC: Aminosalicylic acid and similar agents • A10AD: Insulins and analogues for injection intermediate-acting combined with fast-acting • C03EA: Low-ceiling diuretics and potassium-sparing agents • C05BA: Heparins or heparinoids for topical use • D02AC: Soft paraffin and fat products • D04AB: Anesthetics for topical use	• BMI (Pre-pregnancy) • Calendar time period • Gestational diabetes • Gestational hypertension • History of VTE • Hyperemesis • Parity • Preeclampsia • Previous stroke • Smoking • Thrombophilia • Vascular disease <u>Adjusted for in pharmacological risk factor analysis</u> • Age (Maternal) • BMI (Pre-pregnancy) • Calendar time period • Co-morbidities • History of VTE • Smoking

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
			• G01AF: Imidazole derivatives • G03CA:Natural and semisynthetic oestrogens, plain • G03DA: Pregnen • J01CA: Penicillins with extended spectrum • J01FA: Macrolides • J07BM: Papillomavirus vaccines • N05BA: Benzodiazepine derivatives • R03AC: Selective beta-2-adrenoceptor agonists • R05DA: Opium alkaloids and derivatives	
Kane 2013 Population-based retrospective cohort study Scotland, UK N=1,475,301 deliveries	N=2,006 deliveries with VTE of any kind in pregnancy and postpartum (1287 antenatal DVT, 498 postnatal DVT, 290 PE. Note some women had VTE at multiple time points or unclassified categories therefore numbers do not add up to 2,006) Women aged 13-48 years	N=1,473,295 deliveries without VTE	• Age (Maternal) • Antenatal haemorrhage • Deprivation • Hypertension • Parity • Preeclampsia • Previous VTE • Year of delivery	• Age (Maternal) • Deprivation • Haemorrhage • Hypertension • Mode of delivery • Parity • Previous VTE • Postnatal DVT • Preeclampsia • Year of delivery

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
Larsen 2005 Nested case-control study Denmark N=71,729 women who had given birth in total cohort	N=129 women with VTE in pregnancy and postpartum	N=258 women without VTE	• Blood groups	• Age (Maternal) • BMI • Clomiphene citrate simulation • Diabetes mellitus • Parity • Smoking
Larsen 2007 Population-based nested case-control study Denmark N=71,729 women who had given birth (same cohort as Larsen 2005)	N=129 women with VTE in pregnancy and postpartum	N=258 women without VTE	• BMI • Smoking	• Age (Maternal) • BMI • Clomiphene citrate simulation • Diabetes mellitus • Parity • Smoking
Lindqvist 1999 Population-based retrospective cohort study Sweden	N=608 women with VTE (308 antenatal VTE, 300 postnatal VTE)	N=114,940 pregnant women without VTE	• Age (Maternal) • Multiple pregnancy • Parity • Preeclampsia • Smoking (Number of cigarettes smoked daily)	• Age (Maternal) • Multiple pregnancy • Parity • Preeclampsia • Smoking

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
N=115,548 women				
Rova 2012 Population-based retrospective cohort study Sweden N=954,532 pregnancies	N=19,194 pregnancies with IVF (32 cases with antenatal VTE)	N=935,338 pregnancies without IVF (160 cases with antenatal VTE)	• Age (Maternal) • BMI • IVF • Fresh IVF not OHSS • Fresh IVF and OHSS • FER-frozen embryo replacement cycle (Fresh IVF refers to IVF/ICSI-intracytoplasmic sperm injection)	• Age (Maternal) • BMI • IVF • Fresh IVF not OHSS • Fresh IVF and OHSS • FER-frozen embryo replacement cycle (Fresh IVF refers to IVF/ICSI-intracytoplasmic sperm injection)
Scheres 2020 Population-based retrospective cohort study Netherlands N= 1,919,918 women	N=710 first VTEs occurring in first pregnancy or up to 3 months postpartum	N=1,919,208 first pregnancies without IVF	• Hypertension in pregnancy • Pre-eclampsia	• Age (maternal) at start of follow-up • Number of pregnancies • Self-reported ancestry
Simpson 2001 Retrospective nested case-control	N=336 women with VTE cases (109 VTE in pregnancy and 256 VTE in postpartum)	N=20,090 women without VTE	• Blood group • BMI • Multiple pregnancy (Number of infants delivered)	• Blood group • BMI • Multiple pregnancy

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
England, UK N=395,335 women in total cohort				
Sultan 2013 Population-based retrospective cohort study UK N=376,154 pregnancies in 280,451 women	N=500 VTE events (215 VTE events in pregnancy; 285 VTE in postpartum period)	N=375,654 pregnancies without VTE	• Age (Maternal) • Acute respiratory tract infection • BMI (pre-pregnancy) • Cancer • Gestational diabetes • Gestational hypertension • Inflammatory bowel disease • Multiple pregnancy (multiple gestation) • Parity • Pre-existing diabetes • Pre-existing hypertension • Smoking • Urinary tract infection • Varicose veins	• Acute systemic infection • Age (Maternal) • BMI (pre-pregnancy) • IBD • Parity • Pre-existing diabetes • Smoking status • Varicose veins
Sultan 2013a Population-based retrospective cohort study	N=176 pregnancies with VTE	N=245,485 pregnancies without VTE	• During hospital admission and after discharge	• Age (Maternal) • BMI (Pre-pregnancy) • Calendar year • Cardiac disease • Gestational diabetes • Gestational infection

Study Study design Country Size of cohort	Cases Number of participants	Controls Number of participants	Potential risk factors examined	Covariables adjusted for
England, UK N=206,785 women with 245,661 pregnancies				• Hyperemesis • Varicose vein
Virkus 2014 Population-based retrospective cohort study Denmark N=1,297,037 pregnancies	N=748 VTE events (433 VTE events in pregnancy; 315 in the postpartum)	N=1,296,289 pregnancies without VTE	• BMI • Hospitalisation • Hyperemesis • Infection • Multiple pregnancy • Pre-eclampsia • Smoking	• Age (Maternal) • Anticoagulation treatment • Assisted reproductive treatment • Calendar-year • Educational status • Medical diseases • Parity • Thrombophilia
Wang 2019 Population-based retrospective cohort study Sweden N=1,000,997 pregnancies	N=1,156 pregnancies with VTE events in antenatal period	N=999,841 pregnancies without antenatal VTE	• Blood group (ABO and RhD) • RBC transfusion history (prior to conception)	• Calendar year • Mother's country of origin • Maternal age • Smoking • Multiple gestation

BMI: body mass index; DVT: deep vein thrombosis; FER: frozen embryo replacement; IBD: inflammatory bowel disease; ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilisation; OHSS: ovarian hyperstimulation syndrome; PE: pulmonary embolism; RBC: red blood cell; VTE: venous thromboembolism

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

There was no economic evidence identified for this review question and therefore there is no excluded studies list in appendix K.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Acute respiratory tract infection

- Very low quality evidence from 1 cohort study (N=280,451 women) showed no important difference in the risk of VTE for women with acute respiratory tract infection during pregnancy: aIRR 1.65 (95% CI 0.94 to 2.90).

Age (Maternal)

- Very low quality evidence from 5 cohort studies and 1 nested case-control study (N=401,369 women, N=1,475,301 deliveries, and N=1,254,342 pregnancies) showed an important increase in the risk of VTE in pregnancy in women aged ≥35 years in 2 studies: age group ≥35 years: DVT aIRR 1.33 (95% CI 1.10 to 1.60); age group ≥40 years: aOR 2.10 (95% CI 1.3 to 3.7). Evidence from 3 other studies showed no important difference in the risk of VTE for women aged ≥35 years: age group ≥35 years: aHR 1.31 (95% CI 0.98 to 1.75); age group ≥35 years: aOR 1.00 (95% CI 0.7 to 1.4); age group 35-44 years: aIRR 1.40 (95% CI 0.99 to 1.96). Meanwhile, evidence from 2 studies showed an important increase in risk of VTE in pregnancy with the increasing age of women: aOR 1.2 (95% CI 1.1 to 1.3) among F5 1691A non-carriers; aIRR 1.06 (95% CI 1.01 to 1.11). The evidence however showed no important difference in the risk of VTE in pregnancy

for women with age groups ≤35 years with effect estimates ranging from 0.89 to 1.45 and 95% CI between 0.5 and 2.62.

Antenatal haemorrhage

- Very low quality evidence from 1 cohort study (N=1,475,301 deliveries) showed an important increase in the risk of VTE in pregnancy for women with antenatal haemorrhage during pregnancy: aIRR 1.34 (95% CI 1.09 to 1.64).

Blood group

- Very low quality evidence from 1 cohort study (N=1,000,997 pregnancies) and 2 nested case-control studies (N=20,813 women) showed an important increase in the risk of VTE in pregnancy in women with blood group A (when O was the reference): Blood group A: aOR 3.9 (95% CI 1.5 to 9.7); blood group A: aOR 1.9 (95% CI 1.2 to 3.0); blood group A: aOR 1.78 (95% CI 1.55 to 2.04).
- Very low quality evidence from 1 cohort study (N=1,000,997 pregnancies) and 2 nested case-control studies (N=20,813 women) showed an important increase in the risk of VTE in in pregnancy in women with blood group B (when O was the reference) in one study and no difference in two studies: Blood group B: aOR 1.64 (95% CI 1.35 to 1.99); blood group B: aOR 1.5 (95% CI 0.4 to 5.5); blood group B: aOR 1.6 (95% CI 0.9 to 2.9)
- Very low quality evidence from 1 cohort study (N=1,000,997 pregnancies) and 2 nested case-control studies (N=20,813 women) showed no difference in the risk of VTE in pregnancy in women with blood group AB (when O was the reference): Blood group AB: aOR 2.2 (95% CI 0.4 to 12.5); blood group AB: aOR 1.6 (95% CI 0.6 to 4.1), blood group AB: 1.20 (95% CI 0.89 to 1.61).
- Low quality evidence from 1 cohort study (N=1,000,997 pregnancies) showed no difference in the risk of VTE in pregnancy in women with blood group RhD- compared to RhD+: aOR 0.96 (95% CI 0.81 to 1.13)

BMI (kg/m^2)

- Very low quality evidence from 2 cohort studies and 3 nested case-control studies (N=26,186 women and 2,251,569 pregnancies) showed an important increase in the risk of VTE in pregnancy in women with a BMI ≥25 in 1 study: aOR 7.4 (95% CI 3.1 to 17.7) F5 1691A non-carriers; aOR 10.5 (95% CI 1.5 to 73.5) F5 1691A carriers. Evidence from 2 studies showed an important increase in the risk of VTE in pregnancy in women with BMI ≥30: BMI>30 aOR 9.7 (95% CI 3.1 to 30.8); BMI ≥30: aOR 3.2 (95% CI 2.2 to 4.6). The remaining evidence showed no difference in the risk of VTE in pregnancy in women irrespective of the BMI category with effect estimates ranging from 0.4 to 1.6 and 95% CI from 0.2 to 4.4: BMI 25-30: aOR 1.6 (95% CI 0.6 to 4.4); BMI≥25-<30: aOR 1.2 (95% CI 0.8 to 1.8); BMI 25-29.99: aOR 1.2 (95% CI 0.8 to 2.0); BMI≥30: aOR 1.4 (95% CI 0.7 to 2.6); BMI 25-29.9: aIRR 1.4 (95% CI 1.0 to 2.0); 30-34.9: aIRR 1.0 (95% CI 0.6 to 1.8); >35: aIRR 0.7 (95% CI 0.3 to 1.8).

Cancer (unspecified)

- Very low quality evidence from 1 cohort study (N=280,451 women) showed no important difference in risk of VTE in women with cancer during pregnancy: aIRR 1.95 (95% CI 0.86 to 4.41).

Deprivation

- Very low quality evidence from 1 cohort study (N=1,475,301 deliveries) showed an important increase in risk of VTE in pregnancy in women from the most deprived quintile:

5th quintile aIRR 1.26 (95% CI 1.06 to 1.49). No other quintile showed an important difference in the risk of VTE in pregnancy (the 1st quintile was the reference): 2nd quintile: aIRR 0.98 (95% CI 0.81 to 1.17); 3rd quintile: aIRR 0.89 (95% CI 0.74 to 1.07); and 4th quintile: aIRR 1.02 (95% CI 0.85 to 1.22).

Gestational diabetes

- Very low quality evidence from 1 cohort study (N=299,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women with gestational diabetes: aHR 1.52 (95% CI 0.84 to 2.74).

Gestational hypertension

- Very low quality evidence from 3 cohort studies (N=2,200,369 women and 299,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women with gestational hypertension: aHR 1.12 (95% CI 0.52 to 2.40); aIRR 0.99 (95% CI 0.36 to 2.72) in 2 studies and an important increase in the risk of VTE in pregnancy in women with hypertension in pregnancy in 1 study: aHR 2.0 (95% CI 1.7 to 2.4).

History of blood transfusion

- Very low quality evidence from 1 cohort study (N=1,000,997 pregnancies) showed an important increase in the risk of VTE in pregnancy in women a history of RBC transfusion prior to conception: aOR 1.41 (95% CI 1.05 to 1.89).

History of VTE

- Very low quality evidence from 2 cohort studies (N=299,810 pregnancies and 1,475,301 deliveries) showed an important increase in the risk of VTE in pregnancy in women with a history of VTE: aHR 72.65 (95% CI 51.17 to 103.15); aIRR 7.97 (95% CI 6.30 to 10.10).

Hospitalisation

- Low quality evidence from 2 cohort studies (N=206,785 women and 1,297,037 pregnancies) showed an important increase in the risk of VTE in pregnancy in women who were hospitalised during pregnancy: <3 days: aIRR 4.05 (95% CI 2.23 to 7.38); ≥3days: aIRR 12.2 (95% CI 6.65 to 22.7); 1-2 days aIRR 10.3 (95% CI 7.9 to 13.4); 3-7 days aIRR 12.2 (95% CI 8.7 to 17.0); 8-14 days aIRR 4.0 (95% CI 2.0 to 7.3); >14 days aIRR 3.3 (95% CI 2.6 to 4.2). The risk of VTE as reported in 1 of the studies was higher in trimesters 1 and 2 compared to trimester 3 for women who were hospitalised.

Hyperemesis

- Low quality evidence from 2 cohort studies (N=1,596,847 pregnancies) showed an important increase in the risk of VTE in pregnancy in women with hyperemesis during pregnancy: aHR 2.40 (95% CI 1.43 to 4.04); aIRR 2.5 (95% CI 1.4 to 4.5).

Infection (unspecified)

- Low quality evidence from 1 cohort study (N=1,297,037 pregnancies) showed an important increase in the risk of VTE in pregnancy in women with infection as a discharge diagnosis or with antibiotic treatment during pregnancy: infection diagnosis: aIRR 4.3 (95% CI 2.7 to 7.1); antibiotic treatment: aIRR 1.8 (95% CI 1.5 to 2.3).

Inflammatory bowel disease

- Very low quality evidence from 2 cohort studies (N=1,327,205 women) showed an important increase in the risk of VTE in pregnancy in women with IBD: aRR 1.61 (95% CI 1.01 to 2.56); aIRR 3.50 (95% CI 1.12 to 10.9).

In-vitro fertilisation

- Very low quality evidence from 1 cohort study (N=954,532 pregnancies) showed an important increase in the risk of VTE during the first trimester in women who received IVF with or without OHSS: fresh IVF not OHSS: aOR 4.7 (95% CI 2.6 to 8.4); fresh IVF and OHSS: aOR 101.0 (95% CI 62.5 to 163.3). However, the evidence also showed no important difference in the risk of first trimester VTE for women who received frozen embryo replacement (FER) cycle: aOR 1.6 (95% CI 0.2 to 11.3).

Medications

- Very low quality evidence from 1 cohort study (N=229,810 pregnancies) showed an important increase in the risk of VTE in pregnancy in women who had been advised to use the following groups of medication:
  - proton pump inhibitors
  - aminosalicylic acid and similar agents
  - insulins and analogues for injection intermediate-acting combined with fast-acting;
  - low-ceiling diuretics and potassium-sparing agents
  - heparins or heparinoids for topical use
  - soft paraffin and fat products
  - anesthetics for topical use
  - imidazole derivatives
  - natural and semisynthetic oestrogens
  - penicillins with extended spectrum
  - macrolides
  - papillomavirus vaccines
  - benzodiazepine derivatives
  - selective beta-2-adrenoceptor agonists
  - opium alkaloids and derivatives.
- Very low quality evidence from 1 cohort study (N=229,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women who had been advised to use the following groups of medication:
  - corticosteroid for local oral treatment
  - combinations and complexes of aluminium
  - calcium and magnesium compounds
  - H2- receptor antagonists and other drugs for peptic ulcer and gastro-oesophageal reflux disease
  - synthetic anticholinergic esters with tertiary amino group;
  - propulsives
  - serotonin (5HT3) antagonist
  - contact laxatives; enemas
  - centrally acting antiobesity products
  - insulins and analogues for injection, fast acting

- insulins and analogues for injection, long acting
- biguanides
- vitamin b-complex, including combinations
- iron bivalent, oral preparations
- vitamin b12 (cyanocobalamin and derivatives)
- folic acid and derivatives
- methyldopa
- thiazides and potassium in combination
- corticosteroids
- beta-blocking agents, plain, selective
- alpha- and beta blocking agents
- other antifungals for topical use
- corticosteroids, weak (group i), moderately potent (group ii); potent (group iii), moderately potent or potent combined with antiseptics, potent combined with antibiotics
- anti-infectives for treatment of acne
- other anti-acne preparations for topical use
- progestogens and estrogens, fixed combinations
- gonadotrophins
- ovulation stimulants, synthetic
- anti gonadotrophin releasing hormones
- glucocorticoids
- thyroid hormones
- sulphur-containing imidazole derivatives
- glycogenolytic hormones
- beta-lactamase sensitive penicillins
- beta-lactamase resistant penicillins
- short-acting sulphonamides
- nitrofuran derivatives
- triazole derivatives
- nucleosides and nucleotides excluding reverse transcriptase inhibitors
- neuraminidase inhibitors
- immunoglobulins, normal human
- other immunosuppressants
- acetic acid derivatives and related substances
- propionic acid derivatives
- other anti-inflammatory/anti-rheumatic agents, non-steroids
- anti-inflammatory preparations, non-steroids for topical use
- natural opium alkaloids
- other opioids
- anilides;
- selective 5HT(1)-receptor agonists
- carboxamide derivatives
- benzodiazepine related drugs
- selective serotonin reuptake inihibitors
- centrally acting sympathomimetics
- drugs used in opioid dependence

- nitroimidazole derivatives
- benzimidazole derivatives
- other antiematodals
- antiallergic agents, excluding corticosteroids
- corticosteroids
- adrenergics and other drugs for obstructive airway diseases
- selective beta-2 adrenoreceptor agonists
- opium derivatives and expectorants
- phenothiazine derivatives
- piperzine derivatives
- other antihistamines for systemic use
- other anti-infectives
- sympathomimetics used as decongestants
- other antiallergic agents
- corticosteroids and anti-infectives used in combination.

Miscarriage

- Low quality evidence from 1 nested case-control study (N=5,370 women) showed an important increase in the risk of VTE in women who miscarried: aOR 96.8 (95% CI 10.2 to 916.7).

Multiple pregnancy

- Very low quality evidence from 3 cohort studies and 1 nested case-control study (N=416,425 women and 1,297,037 pregnancies) showed an important increase in risk of VTE in pregnancy in women with multiple pregnancies from 2 studies: aOR 4.2 (95% CI 1.8 to 9.7); aIRR 2.8 (95% CI 1.9 to 4.2). However, evidence from 2 studies showed no important difference in the risk of VTE in pregnancy for women with multiple pregnancies: aOR 2.10 (95% CI 1.0 to 4.6; aIRR 0.83 (95% CI 0.26 to 2.60).

Parity

- Very low quality evidence from 4 cohort studies (N=395,999 women, 1,475,301 deliveries and 299,810 pregnancies) showed:
  - An important increase in risk of VTE in pregnancy in multiparous women with ≥3 parities (compared to women with single parity) from 1 study: aOR 2.80 (95% CI 1.8 to 4.4) but no important difference in 2 other studies ≥3 versus single parity: aIRR 1.19 (95% CI 0.96 to 1.46), aHR 0.98 (95% CI 0.72 to 1.33) and 1 study of ≥3 versus nulliparity: aIRR 0.89 (95% CI 0.45 to 1.78).
  - No important difference in the risk of VTE in women with 2nd parity (compared to women with single parity) from 2 studies: aHR 0.80 (95% CI 0.61 to 1.06), aOR 1.30 (95% CI 0.8 to 2.0) and no important difference in the risk of VTE in pregnancy in women with 1 or 2 parity (compared to nulliparity) from 1 study: aIRR 0.80 (95% CI 0.71 to 0.90) and no important difference in the risk of VTE in pregnancy in women with 2nd parity compared to nulliparity: aIRR 0.71 (95% CI 0.43 to 1.16)
  - An important increase in risk of VTE in pregnancy for nulliparous women (compared to women with single parity) from 1 study: aOR 2.90 (95% CI 2.1 to 3.9) and an important decrease in risk of VTE in pregnancy for women with single parity compared to nulliparity: aIRR 0.72 (95% CI 0.53 to 0.98)

Pre-eclampsia

- Very low quality evidence from 5 cohort studies (N=2,035,466 women, 1,596,847 pregnancies and 1,475,301 deliveries) showed no important difference in the risk of VTE in pregnancy in women with pre-eclampsia in 4 studies: aOR 0.80 (95% CI 0.4 to 1.6); aHR 1.09 (95% CI 0.58 to 2.04); aIRR 1.03 (95% CI 0.76 to 1.39); aIRR 1.2 (95% CI 0.4 to 3.6) but showed an important increase in the risk of VTE in pregnancy in women with pre-eclampsia in 1 study: aHR 7.8 (95% CI 5.4 to 11.3).

Pre-existing diabetes (unspecified)

- Very low quality evidence from 1 cohort study (N=280,451 women) showed an important increase in the risk of VTE in pregnancy in women with pre-existing diabetes: aIRR 3.54 (95% CI 1.13 to 11.0).

Pre-existing hypertension

- Very low quality evidence from 2 cohort studies (N=280,451 women and 1,475,301 pregnancies) showed no important difference in the risk of VTE in pregnancy in women with pre-existing hypertension: aIRR 1.18 (95% CI 0.96 to 1.44); aIRR 0.74 (95% CI 0.32 to 1.71).

Smoking

- Very low quality evidence from 4 cohort studies and 1 nested case-control study (N=395,999 women and 1,596,847 pregnancies) showed an important increase in the risk of VTE in pregnancy in women who smoked during pregnancy in 1 study: aOR 5.7 (95% CI 2.5 to 13.2). Meanwhile, evidence from 4 studies showed no important difference in the risk of VTE in pregnancy in women who smoked during pregnancy: aHR 1.15 (95% CI 0.87 to 1.52); 1-9 cigarettes: aOR 1.10 (95% CI 0.8 to 1.5); ≥10 cigarettes: aOR 1.30 (95% CI 0.9 to 2.0); aIRR 1.16 (95% CI 0.84 to 1.60); aIRR 0.9 (95% CI 0.7 to 1.2).

Stroke

- Very low quality evidence from 1 cohort study (N=299,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women who had had a stroke before pregnancy: aHR 4.41 (95% CI 0.71 to 27.29).

Thrombophilia (unspecified)

- Very low quality evidence from 1 cohort study (N=299,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women with thrombophilia: aHR 1.30 (95% CI 0.47 to 3.66).

Thrombophilia F2 20210 A (mother)

- Low quality evidence from 1 nested case-control study (N=5,370 women) showed an important increase in the risk of VTE in pregnant women with F2 20210 A thrombophilia during pregnancy: aOR 16.3 (95% CI 6.3 to 42.3).

Thrombophilia F12 46T (mother)

- Low quality evidence from 1 nested case-control study (N=5,370 women) showed an important increase in the risk of VTE in pregnant women with F12 46T thrombophilia during pregnancy: aOR 2.8 (95% CI 1.3 to 5.8).

Thrombophilia PROCR 6936G (mother)

- Very low quality evidence from 1 nested case-control study (N=5,370 women) showed an important increase in the risk of VTE for pregnant women who are non-carriers of the PROCR 6936G thrombophilia (aOR 2.5 (95% CI 1.20 to 5.4) F5 1691A non-carriers), but showed no important difference in the risk of VTE in women who are carriers of the thrombophilia during pregnancy: aOR 0.7 (95% CI 0.1 to 9.9) F5 1691A carriers.

Urinary tract infection

- Very low quality evidence from 1 cohort study (N=280,451 women) showed an important increase in the risk of VTE in pregnancy in women with urinary tract infection during pregnancy: aIRR 1.80 (95% CI 1.22 to 2.67).

Varicose vein

- Very low quality evidence from 1 cohort study (N=280,451 women) showed an important increase in the risk of VTE in pregnancy in women with varicose vein during pregnancy: aIRR 2.21 (95% CI 1.55 to 4.76).

Vascular disease

- Very low quality evidence from 1 cohort study (N=299,810 pregnancies) showed no important difference in the risk of VTE in pregnancy in women with vascular disease before pregnancy: aHR 2.71 (95% CI 0.20 to 37.63).

Year of delivery

- Very low quality evidence from 1 cohort study (N=1,475,301 deliveries) showed an important increase in the risk of VTE in pregnant women based on the year of delivery: aIRR 1.09 (95% CI 1.05 to 1.14). Whilst the evidence showed an increase in the risk of VTE from 2001 to 2005, there was no important difference in the risk of VTE in women who gave birth in years before 2001: 1980 to 2000: 1980-1985: aIRR 1 as reference; 1986-1990: aIRR 0.97 (95% CI 0.82 to 1.15); 1991-1995: aIRR 0.86 (95% CI 0.72 to 1.03); 1996-2000: aIRR 1.00 (95% CI 0.84 to 1.20); 2001-2005: aIRR 1.49 (95% CI 1.26 to 1.76).

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The quality of the evidence

The quality of the evidence in this review was assessed with GRADE and was rated as low to very low. The issues affecting the rating of the quality of the evidence are discussed below.

The risk of bias in studies contributing evidence was assessed with QUIPS checklist. Two studies were of acceptable quality whilst 12 were of low quality. Common issues with the studies with low qualities include not adjusting for important confounders and lack of objective diagnosis of VTE. Hence there were serious risks of bias in the evidence contribution to the outcomes due to study limitations.

The inconsistencies of the evidence contributing to some of the risk factors were also rated as serious to very serious heterogeneity. The risk factors that were rated with serious heterogeneity are age and history of VTE, whilst the risk factors rated with very serious heterogeneity are BMI, gestational hypertension, multiple pregnancy, pre-eclampsia, pre-existing hypertension and smoking.

Evidence for some risk factors was downgraded due to indirectness, either in the population (typically because it only included pregnancies that led to delivery), the outcome (typically because it was not objectively confirmed) or both. The risk factors with indirectness in the population and outcome were deprivation, medications and year of delivery. The risk factors with indirectness in the population alone were acute respiratory infection, antenatal haemorrhage, cancer (unspecified), gestational diabetes, gestational hypertension, history of VTE, history of blood transfusion, IBD, parity, pre-existing diabetes, pre-existing hypertension, stroke, thrombophilia (unspecified), urinary tract infection, vascular disease and varicose veins.

The imprecision of the evidence varied from none to very serious imprecision. The risk factors with serious risk of imprecision are acute respiratory tract infection, antenatal haemorrhage, blood group, cancer (unspecified) deprivation, gestational diabetes, history of blood transfusion, IBD, pre-existing diabetes, smoking and urinary tract infection. The risk factors with very serious risk of imprecision are age, BMI, gestational hypertension, IVF, multiple pregnancy, parity, pre-eclampsia, pre-existing hypertension, stroke, thrombophilia (unspecified), PROCR 6936G mother thrombophilia and vascular disease.

There was also a serious risk of publication bias for the majority of risk factors given that the evidence contributing to them were reported from a small number of studies.

Overall the generally low to very low quality evidence identified as part of this review limited the certainty of the committee in making recommendations. While the committee agreed that assessing overall VTE risk was important and noted some factors that may not always be incorporated into commonly used tools, due to the quality of the evidence available they did not highlight any of these factors within the recommendations themselves.

Evidence of association

The risk factors with a consistent and independent association with increase in risk of VTE in pregnancy were antenatal haemorrhage, blood group A, deprivation, history of VTE, history of blood transfusion, hospitalisation, hyperemesis, infection (unspecified), IBD, some medications (see report for more detail), miscarriage, pre-existing diabetes (unspecified), maternal thrombophilia F2 20210 A, maternal thrombophilia F12 46T, urinary tract infection, varicose vein and year of delivery.

The risk factors with no independent association with increase in risk of VTE were acute respiratory tract infection, cancer (unspecified), gestational diabetes, pre-existing hypertension, Rhesus D+ blood group, stroke, thrombophilia (unspecified), maternal thrombophilia PROCR 6936G and vascular disease.

The risk factors with inconsistent independent association with increase in risk of VTE were age, BMI, blood group B, gestational hypertension, IVF, multiple pregnancy, parity, pre-eclampsia and smoking.

The committee discussed the findings of the review in light of existing UK guidance relating to assessment of VTE risk in pregnant women. There are a variety of published tools that attempt to capture multiple risk factors simultaneously and which suggest thresholds at which prophylaxis should be initiated. The committee agreed that when making decisions about prophylaxis, it is important to capture the entire VTE risk profile of a woman. As this review focused on the impact of each individual risk factor and not the accuracy of any tools overall, the committee agreed to direct healthcare professionals to existing tools but without specifying any specific tool be used. The committee were aware that a commonly used VTE risk tool in the UK is in the Royal College of Obstetricians & Gynaecologists' (RCOG) Green-Top guideline on reducing the risk of venous thromboembolism in pregnancy and while they highlighted it as an example in the recommendations, without having reviewed the evidence for tools overall they were not specifically recommending for or against its use. The committee did note that the RCOG tool was based on a systematic review of the underlying literature, much of which overlapped with the included studies for this report. Although the tool did not validate or specifically report any accuracy, calibration or performance measures of the risk categorisation and treatment algorithm it then derived on the basis of this evidence.

The committee considered whether the evidence was of sufficient strength to highlight any individual factors in the recommendations. Overall they agreed this was not appropriate as it could imply that using single factors (as opposed to a multifactorial tool and overall clinical impression) was sufficient to guide decision making. The committee noted that the reasons why some pregnant women develop VTE is incompletely understood, and is likely to be due to a combination of factors, some recognised and some not. Decision making about risk of VTE and need for thromboprophylaxis should recognise these uncertainties, and also reflect that risks relating to continuous variables such as age or BMI are divided into discrete variables for purposes of research and guideline writing, but that in clinical practice the absolute difference in risk for a woman just below or above a threshold may be very similar. Healthcare practitioners should be aware of this when they discuss risk with women, allowing for individualisation of decision making. While the committee did not highlight any individual factors in the recommendations, they did note some factors in this discussion that appeared to be associated with VTE and are not always incorporated into existing risk tools.

One of these factors was blood group. The evidence showed that being blood group A, and to a similar but less consistently observed extent blood group B, represented a significantly increased risk compared with being blood group O. While the evidence around blood group A consistently showed an important increase in risk compared with group O, for blood group B two of the three included studies found no association. However this likely related to the statistical uncertainty in those outcomes (the wide confidence intervals) as opposed to definitive evidence of no difference. The 3 studies were not meta-analysed as they adjusted for different confounders but on balance the committee agreed the evidence likely represented an important increase in risk with blood group B and group A. This represents a substantial majority of the UK population and the committee were clear that this alone would not be an indication for thromboprophylaxis but could help inform the overall risk profile. The committee chose not to specifically include a recommendation on blood group due to remaining uncertainty in the underlying evidence and to avoid healthcare professionals erroneously using blood group as the sole basis for thromboprophylaxis.

The committee also highlighted that miscarriage in pregnancy appeared to be a risk factor for VTE. This factor is not commonly part of existing risk tools, particularly because risk tools are typically designed to be used during the course of pregnancy as opposed to following a miscarriage. There were concerns regarding the quality of the single study reporting on this risk factor, miscarriage was not the focus of the study (which was investigating the impact of certain genotypes and DVT) and the temporal relationship between miscarriage and VTE was not clear making it difficult to make practical recommendations about how this information could be utilised by users of a guideline for antenatal care. Overall the committee agreed not to specifically include a recommendation on this risk factor because this goes beyond the remit of antenatal care.

The committee discussed the finding that a history of red blood cell transfusion prior to conception or at birth appeared to be associated with an increased risk of VTE. They noted that transfusion during pregnancy was not found by the study to be a risk factor, but there were only a very small number of transfusions during pregnancy (compared with prior to pregnancy or at birth) and the discrepancy was likely to be related to sample size. There was no biologically plausible reason to expect there to be a difference in risk of VTE from a transfusion prior to conception or at birth to one during pregnancy. The committee noted that transfusion during labour is a risk factor that is commonly included in VTE tools like that of the RCOG. Overall the committee agreed that the risk associated with transfusions prior to conception (the study contributing this data was published after the RCOG risk tool) was not of a sufficient magnitude or certainty to warrant highlighting specifically in a separate recommendation, though it may well be a factor for future risk tool research to include or assess.

Some factors not seen to have an important association with VTE in this review likely represent an absence of evidence in the pregnant population as opposed to a true absence of effect in this population. The committee agreed it is biologically implausible to expect known VTE risk factors such as smoking, increased BMI, older age and cancer not to be associated with risk in pregnant women.

Some of the factors found in this review to be an important risk were clearly not relevant to recommendation making, for example the year of birth. The committee reviewed the evidence relating to individual medications. The committee highlighted that many of the medications that appeared to be associated with an increased risk of VTE were those that are prescribed for conditions associated with dehydration or immobility therefore there was likely some residual confounding. Overall the committee agreed that whilst some medications are associated with an increased risk of VTE there were no specific medications that warranted highlighting in this report. Where there has been shown to be a persistent and genuine increased risk of VTE with prescription medication, this will be documented in the summary of product characteristics and the British National Formulary.

The NICE guideline on venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism recommends risk assessment for pregnant women admitted to hospital or a midwife-led unit, however, it does not cover VTE risk assessment in pregnant women in other circumstances. The committee therefore agreed that routine assessing risk factors for VTE should be done at booking appointment, after any hospital admission or significant health event during pregnancy. Management of an increased risk of VTE was not covered by this evidence review, however, the committee agreed via informal consensus that a referral to an obstetrician should be considered for those assessed at having risk factors for VTE so that an appropriate management plan can be made.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

No resource impact is anticipated as the recommendations are current practice. Women are already assessed, using tools published by UK bodies, at their first appointment for their risk of VTE.

The scope of this review only covers identifying risk factors for VTE and not the care pathway once this risk has been identified. Such care pathways can be expensive. If more women are identified as having such risk factors there may be an increase in costs in the short term but these will be balanced against decreased costs and increased quality of life from improved pregnancy outcomes. However, as this recommendation reflects current practice the increase in the number of women identified, if any, will be very small.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Review question	What are the risk factors for venous thromboembolism (VTE) in pregnant women?
Type of review question	Risk factors review
Objective of the review	Although the absolute risk of VTE in pregnancy is relative low, it is one of the main causes of maternal mortality and morbidity in developing countries. The aim of this review is to identify the risk factors in pregnant women associated with the development of venous thromboembolism during pregnancy.
Eligibility criteria – population	All pregnant women who are not receiving thromboprophylactic treatment
Eligibility criteria – risk factor(s)	Maternal and/or pregnancy-related risk factors associated with the development of venous thromboembolism during pregnancy.
Eligibility criteria – Confounding factor(s)	Only analyses that adjust for confounding factors using appropriate type of regression to conduct multivariable analysis will be included and data on the factors adjusted for will be extracted. Studies that only report unadjusted data will be excluded.
Outcomes and prioritisation	• Venous thromboembolism during pregnancy Note: Diagnosis of VTE should be based on imaging in addition to clinical diagnosis. If study does not confirm diagnosis by imaging then the risk of bias for the study regarding outcome assessment will be assessed as at high risk since many people who have clinical symptoms will not develop VTE. Odds or risk ratios for the association of a potential risk factor with VTE will be analysed separately and data for DVT, PE and other forms of VTE will be pooled. Adjusted estimates will be used if both unadjusted and adjusted results are reported. If a study does not report odds ratios, these will be calculated if there is sufficient data to construct a 2x2 table.
Eligibility criteria – study design	INCLUDE: • Systematic reviews of observational studies • Population-based or multi-centre prospective cohort studies • Population-based or multi-centre retrospective cohort studies • Case-control studies nested within cohort of known size only where there has been objective assessment of risk factors Note: results from prospective cohort studies will be prioritised by the committee over other study designs in their decision making.
Other inclusion exclusion criteria	**Exclusion** POPULATION: • Women receiving heparin or warfarin anti-coagulant STUDY DESIGN:

Field (based on PRISMA-P)	Content
	• Before and after studies • Cross-sectional studies • Non-comparative studies • Non-nested case-control studies • Randomised or non-randomised controlled trials (individual or cluster) PUBLICATION STATUS: • Conference abstract LANGUAGE: • Non-English **Inclusion** COUNTRY: • No restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Data from studies conducted in specific populations (for example, specific ethnic groups) will be presented separately. In the presence of heterogeneity, subgroup analysis will be performed according to the trimester (i.e. first; second; third) in which the samples were assessed.
Selection process – duplicate screening/selection /analysis	Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	NGA STAR software will be used to generate bibliographies/citations, and to conduct study sifting and data extraction. Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). For details please see the Supplement 1: methods.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Date limit: 1980 (valid non-invasive VTE tests introduced) • Apply standard animal/non-English language exclusion • All results will be downloaded.
Identify if an update	This antenatal care update will replace the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) which will be taken down in due course. The following recommendations are on air travel during pregnancy from previous antenatal care guidelines of uncomplicated pregnancies (CG 62) first published in 2008: 1.3.12 Air travel during pregnancy 1.3.12.1 Pregnant women should be informed that long-haul air travel is associated with an increased risk of venous thrombosis, although whether or not there is additional risk during pregnancy is unclear. In the general population, wearing correctly fitted compression stockings is effective at reducing the risk.
Author contacts	Developer: National Guideline Alliance.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • ROBIS for systematic reviews of prognostic factor studies • QUIPS checklist v.2 for univariate prognostic factor studies For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/. For further details as to how GRADE will be adapted, see the following article: • Huguet, A., Hayden, J. A., Stinson, J., McGrath, P. J., Chambers, C. T., Tougas, M. E., & Wozney, L. (2013). Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Systematic reviews, 2(1), 71.
Criteria for quantitative synthesis (where suitable)	Meta-analysis of a risk factor will be conducted if the definitions used by the included studies are consistent and the data allows use of the same effect estimate (e.g. odds ratio and related 95% CIs).
Methods for analysis – combining studies and exploring (in)consistency	The adjusted Risk Ratio or Odds Ratio and 95% confidence intervals will be plotted in RevMan if appropriate, although the results for each relative measure will be presented separately. Results will be plotted using RevMan software using the generic inverse variance method and a fixed or random effects model as appropriate. Statistical heterogeneity will be assessed using the I^2 statistic, with $I^2 \geq 50\%$ indicating serious heterogeneity and $i^2 \geq 80\%$ indicating very serious heterogeneity. For more details please see the Supplement 1: methods.
Meta-bias assessment – publication bias, selective reporting bias	For details please see the Supplement 1: methods and section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Kate Harding in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-

Field (based on PRISMA-P)	Content
authors and guarantor	analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the Supplement 1: methods.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	This protocol is not registered with PROSPERO.

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; DVT: deep vein thrombosis; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; PE: pulmonary embolism; RCT: randomised controlled trial; VTE: venous thromboembolism

Appendix B – Literature search strategies

Literature search strategies for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Database(s): Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2020 September 03, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to September 03, 2020
Date of last search: 4th September 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	(Pregnancy/ or Pregnant Women/) use ppez
2	(pregnancy/ or pregnant woman/) use emczd
3	(Prenatal Care/ or Prenatal Diagnosis/) use ppez
4	(prenatal care/ or prenatal diagnosis/) use emczd
5	(antenatal$ or ante-natal$ or ante natal$ or prenatal$ or pre-natal$ or pre natal$ or pregnan$).tw,kw.
6	1 or 2 or 3 or 4 or 5
7	Venous Thrombosis/ use ppez
8	Venous Thromboembolism/ use ppez
9	Thromboembolism/ use ppez
10	Pulmonary Embolism/ use ppez
11	Upper Extremity Deep Vein Thrombosis/ use ppez
12	vein thrombosis/ use emczd
13	venous thromboembolism/ use emczd
14	thromboembolism/ use emczd
15	lung embolism/ use emczd
16	upper extremity deep vein thrombosis/ use emczd
17	((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.
18	((low$ limb$ or femoral$ or iliac$ or inferior vena cava or cerebral$ or sinus$ or axill$ or subclav$) adj (thrombosis or thromboses or thrombus or thromboembolism)).tw,kw.
19	((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz$ or thromboembolism)).tw,kw.
20	(dvt or vte).tw,kw.
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	(Risk Factors/ or Risk Assessment/) use ppez
23	(risk factor/ or risk assessment/) use emczd
24	((risk$ or predict$ or prognos$) adj4 (tool$ or rule$ or index$ or indices or score$ or scoring or scale$ or model$ or system$ or algorithm$ or stratif$ or criteria or calculat$)).tw,kw.
25	(risk$ adj2 (factor$ or assess$)).tw,kw.
26	Needs Assessment/ use ppez
27	needs assessment/ use emczd
28	(need$ adj2 assessment$).tw,kw.
29	(assessment$ adj3 tool$).tw,kw.
30	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	6 and 21 and 30
32	letter/
33	editorial/
34	news/
35	exp historical article/
36	Anecdotes as Topic/
37	comment/
38	case report/
39	(letter or comment*).ti.
40	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	randomized controlled trial/ or random*.ti,ab.
42	40 not 41
43	animals/ not humans/
44	exp Animals, Laboratory/
45	exp Animal Experimentation/
46	exp Models, Animal/
47	exp Rodentia/
48	(rat or rats or mouse or mice).ti.
49	42 or 43 or 44 or 45 or 46 or 47 or 48
50	letter.pt. or letter/
51	note.pt.

#	Searches
52	editorial.pt.
53	case report/ or case study/
54	(letter or comment*).ti.
55	50 or 51 or 52 or 53 or 54
56	randomized controlled trial/ or random*.ti,ab.
57	55 not 56
58	animal/ not human/
59	nonhuman/
60	exp Animal Experiment/
61	exp Experimental Animal/
62	animal model/
63	exp Rodent/
64	(rat or rats or mouse or mice).ti.
65	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66	49 use ppez
67	65 use emczd
68	66 or 67
69	31 and 68
70	31 not 69
71	limit 70 to english language
72	limit 71 to yr="1980 -Current"

Database(s): Cochrane Library
Last searched on **Cochrane Database of Systematic Reviews**, Issue 9 of 12, September 2020, **Cochrane Central Register of Controlled Trials**, Issue 9 of 12, September 2020
Date of last search: 4th September 2020

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Pregnant Women] this term only
#3	MeSH descriptor: [Prenatal Care] this term only
#4	MeSH descriptor: [Prenatal Diagnosis] this term only
#5	((antenatal* or ante-natal* or ante natal* or prenatal* or pre-natal* or pre natal* or pregnan*)):ti,ab,kw (Word variations have been searched)
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH descriptor: [Venous Thrombosis] this term only
#8	MeSH descriptor: [Venous Thromboembolism] this term only
#9	MeSH descriptor: [Thromboembolism] this term only
#10	MeSH descriptor: [Pulmonary Embolism] this term only
#11	MeSH descriptor: [Upper Extremity Deep Vein Thrombosis] this term only
#12	(((venous or vein) NEXT (thrombosis or thromboses or thrombus or thromboembolism))):ti,ab,kw
#13	(((low* limb* or femoral* or iliac* or inferior vena cava or cerebral* or sinus* or axill* or subclav*) NEXT (thrombosis or thromboses or thrombus or thromboembolism))):ti,ab,kw
#14	(((pulmonary or lung) NEAR/3 (embolism or emboli or embolus or emboliz* or thromboembolism))):ti,ab,kw
#15	((dvt or vte)):ti,ab,kw
#16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	MeSH descriptor: [Risk Factors] this term only
#18	MeSH descriptor: [Risk Assessment] this term only
#19	MeSH descriptor: [Needs Assessment] this term only
#20	(((risk* or predict* or prognos*) NEAR/4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*))):ti,ab,kw
#21	((risk* NEAR/2 (factor* or assess*))):ti,ab,kw
#22	((need* NEAR/2 assessment*)):ti,ab,kw
#23	((assessment* NEAR/3 tool*)):ti,ab,kw
#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#6 AND #16 AND #24 Publication Year from 1980 to current

Database(s): CRD: Database of Abstracts of Reviews of Effects (DARE), HTA Database
Date of last search: 4th September 2020

#	Searches
1	MeSH DESCRIPTOR pregnancy EXPLODE ALL TREES IN DARE,HTA
2	MeSH DESCRIPTOR pregnant women EXPLODE ALL TREES IN DARE,HTA
3	MeSH DESCRIPTOR prenatal care EXPLODE ALL TREES IN DARE,HTA
4	MeSH DESCRIPTOR prenatal diagnosis EXPLODE ALL TREES IN DARE,HTA
5	((antenatal* or ante-natal* or ante natal* or prenatal* or pre-natal* or pre natal* or pregnan*)) IN DARE, HTA
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES IN DARE,HTA
8	MeSH DESCRIPTOR Venous Thromboembolism EXPLODE ALL TREES IN DARE,HTA
9	MeSH DESCRIPTOR Thromboembolism EXPLODE ALL TREES IN DARE,HTA

#	Searches
10	MeSH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES IN DARE,HTA
11	MeSH DESCRIPTOR Upper Extremity Deep Vein Thrombosis EXPLODE ALL TREES IN DARE,HTA
12	((((venous or vein) NEAR (thrombosis or thromboses or thrombus or thromboembolism)))) IN DARE, HTA
13	((((low* limb* or femoral* or iliac* or inferior vena cava or cerebral* or sinus* or axill* or subclav*) NEAR (thrombosis or thromboses or thrombus or thromboembolism)))) IN DARE, HTA
14	((((pulmonary or lung) NEAR (embolism or emboli or embolus or emboliz* or thromboembolism)))) IN DARE, HTA
15	(((dvt or vte))) IN DARE, HTA
16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Risk Factors EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Risk Assessment EXPLODE ALL TREES IN DARE,HTA
19	MeSH DESCRIPTOR Needs Assessment EXPLODE ALL TREES IN DARE,HTA
20	((((risk* or predict* or prognos*) NEAR (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)))) IN DARE, HTA
21	(((risk* NEAR (factor* or assess*)))) IN DARE, HTA
22	(((need* NEAR assessment*))) IN DARE, HTA
23	(((assessment* NEAR tool*))) IN DARE, HTA
24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#6 AND #16 AND #24 Publication Year from 1980 to current

Database(s): Cinahl Plus

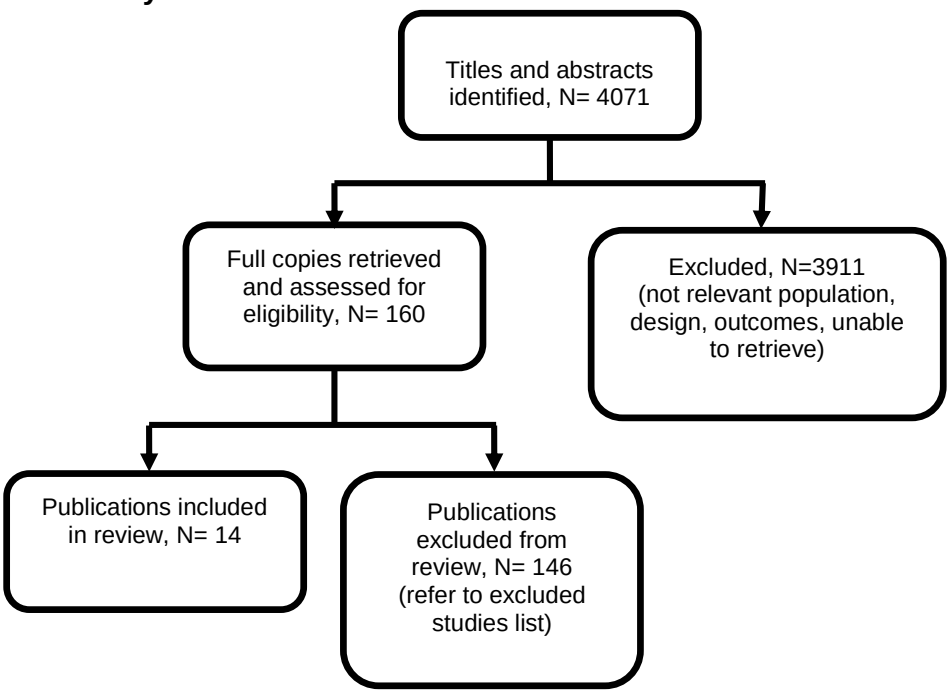
Date of last search: 4th September 2020

#	Searches
S25	S22 NOT S23 Limiters - Publication Year: 1980-2020; English Language;
S23	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S22	S5 AND S14 AND S21
S21	S15 OR S16 OR S17 OR S18 OR S19 OR S20
S20	TI (assessment* N3 tool*) OR AB (assessment* N3 tool*)
S19	TI (need* N2 assessment*) OR AB (need* N2 assessment*)
S18	(MH "Needs Assessment")
S17	TI (risk* N2 (factor* or assess*)) OR AB (risk* N2 (factor* or assess*))
S16	TI ((risk* or predict* or prognos*) N4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)) OR AB ((risk* or predict* or prognos*) N4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*))
S15	(MH "Risk Assessment") OR (MH "Risk Factors")
S14	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13	TI (dvt or vte) OR AB (dvt or vte)
S12	TI ((pulmonary or lung) N3 (embolism or emboli or embolus or emboliz* or thromboembolism)) OR AB ((pulmonary or lung) N3 (embolism or emboli or embolus or emboliz* or thromboembolism))
S11	TI ((low* limb* or femoral* or iliac* or inferior vena cava or cerebral* or sinus* or axill* or subclav*) N1 (thrombosis or thromboses or thrombus or thromboembolism)) OR AB ((low* limb* or femoral* or iliac* or inferior vena cava or cerebral* or sinus* or axill* or subclav*) N1 (thrombosis or thromboses or thrombus or thromboembolism))
S10	TI ((venous or vein) N1 (thrombosis or thromboses or thrombus or thromboembolism)) OR AB ((venous or vein) N1 (thrombosis or thromboses or thrombus or thromboembolism))
S9	(MH "Upper Extremity Deep Vein Thrombosis")
S8	(MH "Pulmonary Embolism")
S7	(MH "Thromboembolism")
S6	(MH "Venous Thromboembolism") OR (MH "Venous Thrombosis")
S5	S1 OR S2 OR S3 OR S4
S4	TI (antenatal* or ante-natal* or ante natal* or prenatal* or pre-natal* or pre natal* or pregnan*) OR AB (antenatal* or ante-natal* or ante natal* or prenatal* or pre-natal* or pre natal* or pregnan*)
S3	(MH "Prenatal Care") OR (MH "Prenatal Diagnosis")
S2	(MH "Expectant Mothers")
S1	(MH "Pregnancy")

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Table 4: Clinical evidence tables

Study details	Participants	Factors and results	Comments
Full citation Galanaud,J.P., Cochery-Nouvellon,E., Alonso,S., Chauleur,C., Mercier,E., Lissalde-Lavigne,G., Fabbro-Peray,P., Reny,J.L., Mares,P., Dauzat,M., Quere,I., Gris,J.C., Paternal endothelial protein C receptor 219Gly variant as a mild and limited risk factor for deep vein thrombosis during pregnancy, Journal of Thrombosis and Haemostasis, 8, 707-713, 2010 **Ref Id** 125182 **Country/ies where the study was carried out** France **Study type** population-based Nested case-control study **Study dates**	**Cases** 66 with DVT (46 in pregnancy, 20 in postpartum) **Diagnostic criteria** Objective diagnosis **Controls** 5304 without DVT **Inclusion criteria** • Women with first symptomatic VTE (DVT or PE) confirmed by compression ultrasound of the whole leg (DVT) or lung perfusion scintigraphy or helical CT scan (PE). • Controls were women free of VTE, selected by random from the same cohort. **Exclusion criteria**	**Factors** VTE was defined as DVT or PE confirmed using ultrasound of the whole leg (suspected DVT) or lung perfusion scintigraphy or helical CT scan (suspected PE). Risk factors considered (included in the multivariate model if p >0.10 in univariate analysis): • age • overweight (BMI >25) • late miscarriage (spontaneous interruption of pregnancy after 10 weeks of gestation, confirmed by home pregnancy test, blood beta human chorionic gonadotropin analysis or ultrasound) • pre-eclampsia (defined as gravidic hypertension after 20 weeks of pregnancy [systolic BP >140 mmHg, diastolic BP >90 mmHg, a rise in systolic BP over 30 mmHg or rise in diastolic BP over 15 mmHg on at least two occasions 6h apart from each other], and proteinuria >300 mg per 24h) • Caesarean section • twin pregnancy • conceptus weight (values adjusted for term of delivery)	**Limitations** **QUIPS checklist** Study participation: Low risk (random selection of an unmatched control used, power calculation not performed, unlikely to introduce substantial bias). Study attrition: Low risk (attrition not an issue given study based on data an ongoing prospective cohort study) Prognostic factor measurement: low risk (unsure if method and setting is the same for all participants, unlikely to introduce substantial bias). Outcome measurement: Low risk (VTE measured objectively, unsure if method and setting is the same for all participants, unlikely to introduce substantial bias) Study confounding: High risk (smoking was not adjusted for, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantial bias). Statistical analysis and reporting: Low risk (no areas of concern for this domain). **Overall quality: Low** **Other information** NOTE: only result for DVT was reported.

Study details	Participants	Factors and results	Comments

January 1999 onwards (end date not reported)
 	
Consecutive recruitment
 	
Yes
 	
Funding
Diagnostica Stago, Baxter Healthcare Corporation, Aventis pharmaceutical industry.
	• A personal or a first-degree relative history of VTE or of superficial vein thrombosis
	• Chronic treatment interfering with the haemostatic system, including daily aspirin doses >250 mg.
	
	Statistical method
	
	• Step-by-step multivariate logistic regression models to estimate adjusted odds ratios and 95% CI associated with each risk factor for VTE during pregnancy.
	• Any variable with a p-value of ≤0.10 on univariate analysis was included in the multivariate models.
	• No power calculation performed.
	
	Demographics
	Total population
	N=5370 out of 33,238 consecutive primigravidae
	Age
	
	• With VTE: Median 31 (Q1-Q3 29-34); Without VTE Median 28 (Q1-Q3 24-32)
	
	Parity
	
	• Primigravidae
		• bed confinement (bed or armchair confinement for more than 6h per day)
		• trauma or recent plaster immobilisation of the lower extremities
		• recent travel (travel >3h in the last month - note, does not mention if this means flight travel)
		• surgery in the previous 45 days
		• infectious disease (fever, or biological, bacteriological or radiological signs of infection that medical doctor considers infectious and introduces antiobiotic therapy)
		• genetic characteristics for both mother and father:
		  ○ PROCR 6936G
		  ○ F5 1691A
		  ○ F2 20210A
		  ○ F12 46T
		
		Adjusted relative risk/odds ratio
		With VTE n=66 (iliac VTE n=31, infra-iliac DVT n=35), controls without VTE n=5304
		
		• VTE during pregnancy n=46
		• VTE in the postpartum period n=20
		
		Please note that the below includes those with VTE in the postpartum period.
		Multivariate analysis of the association between maternal weight and VTE during pregnancy. Adjusted odds ratio (aOR) that controlled for age, overweight, miscarriage after 10 weeks of gestation, conceptus weight, maternal F5 1691A, maternal F2 20210A, maternal F12 46T, maternal PROCR 6936G, paternal PROCR 6936G, and interaction between maternal F5 1691A and paternal PROCR 6936G.	

Study details	Participants	Factors and results	Comments
	Overweight (BMI >25) • With VTE 43/66; Without VTE 1931/5304 **Late miscarriage (>10 weeks of gestation)** • With VTE 7/66; Without VTE 12/5304 **Pre-eclampsia** • With VTE 0/66; Without VTE 53/5304 **Twin pregnancy** • With VTE 2/66; Without VTE 53/5304	**DVT - among women who are F5 1691A non-carriers** **Maternal age (continuous, risk expressed for the increase of one unit for age)** • aOR 1.2 (95% CI: 1.1-1.3) **Overweight (BMI >25)** • BMI ≤25: reference • BMI >25: aOR 7.4 (95% CI: 3.1-17.7) **Miscarriage (>10 weeks of gestation)** • No miscarriage: reference • Miscarriage: aOR 96.8 (95% CI: 10.2-916.7) **Conceptus weight (continuous, risk expressed for the decrease of one unit for conceptus weight)** • aOR 1.07 (95% CI: 1.05-1.10) **F2 20210A (mother)** • No F2 20210A (mother): reference • F2 20210A (mother): aOR 16.3 (95% CI: 6.3-42.3) **F12 46T (mother)** • No F12 46T (mother): reference • F12 46T (mother): aOR 2.8 (95% CI: 1.3-5.8)	

Study details	Participants	Factors and results	Comments
		PROCR 6936G (mother) • No PROCR 6936G (mother): reference • PROCR 6936G (mother): aOR 2.5 (95% CI: 1.2-5.4) **PROCR 6936G (father)** • No PROCR 6936G (father): reference • PROCR 6936G (father): aOR 1.2 (95% CI: 0.5-2.9) **DVT - among women who are F5 1691A carriers** **Overweight (BMI >25)** • BMI ≤25: reference • BMI >25: aOR 10.5 (95% CI: 1.5-73.5) **Conceptus weight (continuous, risk expressed for the decrease of one unit for conceptus weight)** • aOR 1.1 (95% CI: 1.0-1.2) **PROCR 6936G (mother)** • No PROCR 6936G (mother): reference • PROCR 6936G (mother): aOR 0.7 (95% CI: 0.1-9.9) **PROCR 6936G (father)** • No PROCR 6936G (father): reference	

Study details	Participants	Factors and results	Comments
		• PROCR 6936G (father): aOR 19.7 (95% CI: 2.8-137.2) **Iliac DVT - among women who are F5 1691A non-carriers** Maternal age (continuous, risk expressed for the increase of one unit for age) • aOR 1.2 (95% CI: 1.0-1.4) Overweight (BMI >25) • BMI ≤25: reference • BMI >25: aOR 10.2 (95% CI: 2.2-46.9) Conceptus weight (continuous, risk expressed for the decrease of one unit for conceptus weight) • aOR 1.1 (95% CI: 1.0-1.1) F2 20210A (mother) • No F2 20210A (mother): reference • F2 20210A (mother): aOR 20.1 (95% CI: 4.9-82.4) PROCR 6936G (mother) • No PROCR 6936G (mother): reference • PROCR 6936G (mother): aOR 5.5 (95% CI: 1.7-17.2) PROCR 6936G (father) • No PROCR 6936G (father): reference	

Study details	Participants	Factors and results	Comments
		• PROCR 6936G (father): aOR 1.5 (95% CI: 0.4-5.8) **Iliac DVT - among women who are F5 1691A carriers** Conceptus weight (continuous, risk expressed for the decrease of one unit for conceptus weight) • aOR 1.2 (95% CI: 1.0-1.4) PROCR 6936G (father) • No PROCR 6936G (father): reference • PROCR 6936G (father): aOR 77.6 (95% CI: 4.2->999.9) **Infra-iliac DVT (general)** Maternal age (continuous, risk expressed for the increase of one unit for age) • aOR 1.2 (95% CI: 1.1-1.3) Overweight (BMI >25) • BMI ≤25: reference • BMI >25: aOR 6.5 (95% CI: 2.5-16.8) Miscarriage (>10 weeks of gestation) • No miscarriage: reference • Miscarriage: aOR 201.2 (95% CI: 19.4->999.9)	

Study details	Participants	Factors and results	Comments
		Conceptus weight (continuous, risk expressed for the decrease of one unit for conceptus weight) • aOR 1.09 (95% CI: 1.06-1.12) F5 1691A (mother) • No F5 1691A (mother): reference • F5 1691A (mother): aOR 32.1 (95% CI: 11.2-92.0) F2 20210A (mother) • No F2 20210A (mother): reference • F2 20210A (mother): aOR 15.5 (95% CI: 4.5-53.0) F12 46T (mother) • No F12 46T (mother): reference • F12 46T (mother): aOR 2.7 (95% CI: 1.2-6.2) PROCR 6936G (mother) • No PROCR 6936G (mother): reference • PROCR 6936G (mother): aOR 1.3 (95% CI: 0.5-3.7) PROCR 6936G (father) • No PROCR 6936G (father): reference • PROCR 6936G (father): aOR 1.7 (95% CI: 0.7-4.3)	

Study details	Participants	Factors and results	Comments
Full citation Hansen, A. T., Erichsen, R., Horvath-Puho, E., Sorensen, H. T., Inflammatory bowel disease and venous thromboembolism during pregnancy and the postpartum period, Journal of Thrombosis and Haemostasis, 15, 702-708, 2017 **Ref Id** 999594 **Country/ies where the study was carried out** Denmark **Study type** Population-based retrospective cohort study **Study dates** 01/1980 to 12/2013 **Consecutive recruitment** Yes **Funding** One researcher (H.T. Sorensen) received salary support from Program for Clinical Research Infrastructure (PROCRIN), Lundbeck Foundation, and Novo Nordisk Foundation.	**Cases** 11,978 pregnancies with IBD **Diagnostic criteria** ICD-8 codes up to 1993, or ICD-10 codes thereafter **Controls** 1,966,289 pregnancies without IBD **Inclusion criteria** • Record of delivery in Medical Birth Registry (MBR) between January 1980 to December 2013 • Primary or secondary diagnoses recorded in Danish National Patient Registry (DNPR) between January 1980 to December 2013 **Exclusion criteria** • No primary or secondary diagnosis recorded in DNPR • Emergency room diagnosis only **Statistical method**	**Factors** • Inflammatory bowel disease (IBD); 11,978 pregnancies with IBD, 1,966,723 pregnancies without IBD. • Definition of VTE from ICD-8 or ICD-10 as appropriate and results include both first and recurrent VTE events; includes codes for superficial thrombosis and results include 120 events (3.4% of VTE events in cohort) diagnosed with this. Definitions of factors: Inflammatory bowel disease (IBD) diagnosis defined as date of first hospital admission for IBD or first outpatient clinic visit for IBD before or after conception; women whose IBD diagnosed during pregnancy treated as exposed in current and anu subsequent pregnancy; flare of IBD defined as acute admission during pregnancy with IBD as primary or secondary diagnosis. **Adjusted relative risk/odds ratio** **<u>Inflammatory bowel disease</u>** • aRR 1.67 (95% CI 1.15-2.41), adjusted for maternal age and smoking (all deliveries in Denmark from 1991 to 2013; number of VTE events in IBD group=32; number of VTE events in no IBD group=2496) • aRR 1.61 (95% CI 1.01-2.56), adjusted for maternal age, smoking, and maternal pre-pregnancy BMI (all deliveries in	**Limitations** **<u>QUIPS checklist</u>** Study participation: Low risk (no area of concern for this domain) Study attrition: Low risk (attrition not issue given study based on registry data) Prognostic factor measurement: Moderate risk (BMI measured as pre-pregnancy BMI, incomplete data for smoking and BMI, unsure if method and setting of factor measurement same for all participants, but unlikely to introduce substantive bias) Outcome measurement: High risk (VTE events not identified objectively, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantial bias) Study confounding: High risk (results adjusted for 2-3 covariates, use of thromboprophylaxis and other drugs used for IBD, very likely to introduce substantive bias) Statistical analysis and reporting: Low risk (partial concerns regarding description of regression model). **Overall quality: Low** **Other information** • Reported adjusted RR for postpartum VTE, data not extracted reported • Record for smoking became only available in 1991 • Pre-pregnancy BMI reported

Study details	Participants	Factors and results	Comments
	• Crude and adjusted relative risks with 95% CIs estimated using modified Poisson regression relative to prognostic factors of inflammatory bowel disease (IBD). • Two adjusted models used for estimating risk of VTE during pregnancy. **Demographics** **<u>Total number of women</u>** N=1,046,754 **<u>Maternal age at delivery</u>** • 12-29 years-old: IBD=5372 (44.8%); No IBD=1,106,795 • 30-34 years-old: IBD=4361 (36.4%); No IBD=595,780 • 35+ years-old: IBD=2245 (18.7%); No IBD=264,148 **<u>Parity</u>** • 1: IBD=5264 (43.9%); No IBD=875,679 • 2: IBD=4570 (38.2%); No IBD=713,382 • 3+: IBD=2018 (16.8%); No IBD=358,885 • Missing: IBD=126 (1.1%); No IBD=18,777 **<u>Previous VTE</u>**	Denmark from 2004 to 2013; number of VTE events in IBD group=20; number of VTE events in no IBD group=1234) Note: results include first and recurrent VTE events	

Study details	Participants	Factors and results	Comments
	• IBD: 101 (0.8%); No IBD: 5969 **Smoking (record for smoking became only available in 1991)** • IBD: 1927 (18.3%); No IBD: 286,084 **Maternal pre-pregnancy BMI (kg/m^2)** • <25: IBD=3853 (65.8%); No IBD=371,982 • 25-29: IBD=1111 (19.0%); No IBD= 117,348 • 30+: IBD=624 (10.7%); No IBD= 67,635 • Missing: IBD=269 (4.6%); No IBD=32,095		
Full citation Jensen, T. B., Gerds, T. A., Gron, R., Bretler, D. M., Schmiegelow, M. D., Andersson, C., Azimi, A., Gislason, G., Torp-Pedersen, C., Olesen, J. B., Risk factors for venous thromboembolism during pregnancy, Pharmacoepidemiology & Drug Safety, 22, 1283-91, 2013 **Ref Id** 385569 **Country/ies where the study was carried out**	**Cases** 337 with VTE **Diagnostic criteria** ICD-10 **Controls** 299,473 without VTE **Inclusion criteria** • women aged between 15 and 50 years with pregnancy-related discharge codes in the	**Factors** VTE among pregnant women was defined as either PE or DVT antepartum according to the Danish ICD-10-codes **Non-pharmacological risk factors for VTE** • Age • Parity • Pre-pregnancy BMI • Smoking • Previous of VTE • Stroke • Vascular disease • Thrombophilia • Gestational hypertension	**Limitations** **QUIPS checklist** Study participation: Low risk (only hospitalised cases included, unlikely to introduce substantial bias) Study attrition: Low risk (attrition not an issue given study based on register) Prognostic factor measurement: Moderate risk (BMI was measured with pre-pregnancy weight, unsure if method and setting for measurement is the same for all participants, may likely introduce substantial bias) Outcome measurement: High risk (VTE not identified objectively, antithrombotic agents used by women were excluded from analysis of medications, unsure method

Study details	Participants	Factors and results	Comments
Denmark **Study type** Population-based retrospective cohort study **Study dates** 2003-2010 **Consecutive recruitment** Yes **Funding** • Jensen, T.B received funding by The Lundbeck Foundation.	Medical Birth Register in Denmark with ICD-10 codes, • Hospitalised cases only. • First birth during the study period for each woman with complete data on height, pre-pregnancy weight, smoking status during pregnancy, parity and gestational age at birth. **Exclusion criteria** None stated **Statistical method** • Association of VTE with prognostic factors investigated by univariable and multivariable Cox regression analyses. • Age and parity were never included in the same model. • Pharmacological medications analysed in separate analyses controlling for age, BMI, smoking, history of VTE, co-morbidities, and calendar time period. • a p< 0.05 was significant in all analysis. • Two sensitivity analyses were carried out, 1 including all pregnancies for each woman	• Hyperemesis • Gestational diabetes • Preeclampsia Data for non-pharmacological factors were obtained from the register and no clear definition was provided. **Pharmacological risk factors** • A02BC: Proton pump inhibitors • A07EC: Aminosalicylic acid and similar agents • A10AD: Insulins and analogues for injection intermediate-acting combined with fast-acting • C03EA: Low-ceiling diuretics and potassium-sparing agents • C05BA: Heparins or heparinoids for topical use • D02AC: Soft paraffin and fat products • D04AB: Anesthetics for topical use • G01AF: Imidazole derivatives • G03CA:Natural and semisynthetic estrogens, plain • G03DA: Pregnen • J01CA: Penicillins with extended spectrum • J01FA: Macrolides • J07BM: Papillomavirus vaccines • N05BA: Benzodiazepine derivatives • R03AC: Selective beta-2-adrenoceptor agonists • R05DA: Opium alkaloids and derivatives	and setting of measurement is the same for all participants, very likely to introduce substantial bias) Study confounding: High risk (partial definition of confounders, thromboprophylaxis not adjusted for, unsure method and setting of measurement is the same for all participants, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (partial concern about the description of regression models and presentation of the data for pharmacological data, unlikely to introduce substantial bias) **Overall quality: Low**

Study details	Participants	Factors and results	Comments
	during the study period and another including both in- and out-patient VTE-diagnosis. • Antithrombotic agents ATC: B01 used for the treatment of DVT were excluded from the analyses. **Demographics** **<u>Baseline Characteristics</u>** Total population N=299,810 pregnancies/ women **<u>Age: Mean (SD)</u>:** With VTE=30.1(5.4); Without VTE=29.7(5.0) • <20: With VTE=12; Without VTE=7,875 • 20-<30: With VTE=159; Without VTE=150,430. • 30-<35: With VTE=102; Without VTE=96,710. • ≥35: With VTE=64; Without VTE=44,458. **<u>Parity</u>** • 1: With VTE=214; Without VTE=175,722. • 2: With VTE=71; Without VTE=78,232. • ≥3: With VTE=52; Without VTE=45,519. **<u>Pre-pregnancy BMI</u>**	**Adjusted relative risk/odds ratio** Total number of women with VTE=337; without VTE=299,473 Multivariate Hazard ratio (HR) was calculated for each risk factor and adjusted for age, BMI, smoking, previous VTE, previous stroke, vascular disease, thrombophilia, gestational hypertension, hyperemesis, gestational diabetes, pre-eclampsia, and calendar times period except for parity which are from a model where age has been substituted with parity: **<u>Age:</u>** p=0.216 • <20: aHR-1.45 (95% CI: 0.80-2.62). • 20-<30: aHR-1.00 as reference. • 30-<35: aHR-1.01 (95% CI: 0.78-1.29). • ≥35: aHR-1.31 (95% CI: 0.98-1.75). **<u>Parity</u>** • 1: With VTE=214; Without VTE=175,722. • 2: With VTE=71; Without VTE=78,232. • ≥3: With VTE=52; Without VTE=45,519. **<u>Pre-pregnancy BMI</u>** • <18.5: With VTE=11; Without VTE=20,605. • 18.5-<25: With VTE=19; Without VTE=183,495. • 25-<30: With VTE=88; Without VTE=61,641. • ≥30: With VTE=47; Without VTE=33,732 **<u>Smoking</u>**	

Study details	Participants	Factors and results	Comments
	• <18.5: With VTE=11; Without VTE=20,605. • 18.5-<25: With VTE=19; Without VTE=183,495. • 25-<30: With VTE=88; Without VTE=61,641. • ≥30: With VTE=47; Without VTE=33,732. **Smoking** • Smoking: With VTE=61; Without VTE=48,785. • Not-smoking: With VTE=276; Without VTE=250,688. **Previous of VTE** • Previous VTE=40; Without Previous VTE=500 • Previous PE=8; Without Previous PE=109. • Previous DVT=34; Without Previous DVT=409 **Co-morbidity (n)** Before pregnancy **Atrial fibrillation**: With VTE=0; Without VTE=122 **Stroke:** With VTE=2; Without VTE=151 **Vascular disease:** With VTE: 1; Without VTE=30 **Valvular disease:** With VTE=0; Without VTE=35 **Thrombophilia:** With VTE=4; Without VTE=153	• Smoking: aHR-1.15 (95% CI: 0.87-1.52). • Not-smoking: HR-1.0 as reference. **Previous VTE:** • aHR-72.65 (95% CI: 51.17-103.15). **Stroke:** • aHR-4.41 (95% CI: 0.71-27.29). **Vascular disease:** • aHR-2.71 (95% CI: 0.20-37.63). **Thrombophilia:** • aHR-1.30 (95% CI: 0.47-3.66). **Gestational hypertension:** • aHR-1.12 (95% CI: 0.52-2.40). **Hyperemesis:** • aHR-2.40 (95% CI: 1.43-4.04). **Gestational diabetes:** • aHR-1.52 (95% CI: 0.84-2.74). **Preeclampsia:**	

Study details	Participants	Factors and results	Comments
	Cancer: With VTE=0; Without VTE=433 **Nephrotic syndrome:** With VTE=0; Without VTE=12 **Hypertension:** With VTE=0; Without VTE=437 ***During pregnancy*** **Gestational hypertension:** With VTE=7; Without VTE=50 **Hyperemesis:** With VTE=15; Without VTE=5382 **Gestational diabetes:** With VTE=12; Without VTE=6456 **Pre-eclampsia:** With VTE=11; Without VTE=8840	• aHR-1.09 (95% CI: 0.58-2.04). N.B: Sensitivity analysis did not change any conclusions **Risk factors associated with redeemed medications** (adjusted for age, BMI, smoking, history of VTE, co-morbidities, and calendar time period). • A01AC: Corticosteroids for local treatment: aHR=6.48 (95% CI 0.91-46.28), p-value=0.222 • A02AD: Combinations and complexes of aluminium, calcium and magnesium compounds: aHR=1.13 (95% CI 0.16-8.09), p-value= 0.939 • A02BA: H2-receptor antagonists: aHR=2.21 (95% CI 0.82-5.95), p-value=0.310 • A02BC: Proton pump inhibitors: aHR=2.58 (95% CI 1.47-4.53), p-value=0.012 • A02BX: Other drugs peptic ulcer and gastro-oesophageal reflux disease: aHR=2.24 (95% CI 0.31-15.95), p-value=0.581 • A03AA: Synt anticholinergic, esters with tertiary amino group: aHR=12.96 (95% CI 1.82-92.33), p-value=0.060 • A03FA: Propulsives: aHR=1.36 (95% CI 0.85-2.20), p-value=0.426 • A04AA: Serotonin (5HT3) antgonists: aHR=1.67 (95% CI 0.56-4.99), p-value=0.537 • A06AB: Contact laxatives: aHR=2.11 (95% CI 0.28-16.02), p-value=0.612 • A06AG: Enemas: aHR=2.92 (95% CI 0.41-21.08), p-value=0.509 • A07AA: Antibiotics: aHR=3.09 (95% CI 0.43-22.01), p-value=0.480	

Study details	Participants	Factors and results	Comments
		• A07EC: Aminosalicylic acid and similar agents: aHR=7.07 (95% CI 2.63-18.99), p-value=0.004 • A08AA: Centrally acting antiobesity products: aHR=4.36 (95% CI 0.60-31.54), p-value=0.371 • A10AB: Insulins and analogues for injections, fast acting: aHR=2.57 (95% CI 0.36-18.51), p-value=0.537 • A10AD: Insulins and analogues for injection intermediate-acting combined with fast-acting: aHR=8.09 (95% CI 1.86-35.13), p-value=0.040 • A10AE: Insulins and analogues for injection, long-acting: aHR=7.79 (95% CI 1.08-56.46), p-value=0.161 • A10BA: Biguanides: aHR=0.58 (95% CI 0.08-4.17), p-value=0.726 • A11E: Vitamin b-complex, including combinations: aHR=5.54 (95% CI 0.77-39.79), p-value=0.277 • B03AA: Iron bivalent, oral preparations: aHR=0.85 (95% CI 0.12-6.03), p-value=0.939 • B03BA: Vitamin B12 (cyanocobalamin and derivatives): aHR=1.35 (95% CI 0.43-4.26), p-value=0.731 • B03BB: Folic acid and derivatives: aHR=1.54 (95% CI 0.38-6.18), p-value=0.678 • C02AB: Methyldopa: aHR=2.24 (95%CI 0.31-16.45), p-value=0.581 • C03AB: Thiazides and potassium in combination: aHR=2.21 (95% CI 0.31-15.79), p-value=0.581 • C03EA: Low-ceiling diuretics and potassium-sparing agents: aHR=39.15 (95% CI 5.44-281.98), p-value=0.006 • C05AA: Corticosteroids: aHR=1.37 (95% CI 0.84-2.24), p-value=0.429	

Study details	Participants	Factors and results	Comments
		• C05BA: Heparins or heparinoids for topical use: aHR=15.75 (95% CI 7.74-32.05), p-value=<0.001 • C07AB: Beta blocking agents: aHR=4.22 (95% CI 0.59-30.16), p-value= 0.371 • C07AG: Alpha- and beta blocking agents: aHR=1.25 (95% CI 0.17-8.98), p-value=0.932 • D01AC: Imidazole and triazole derivatives: aHR=1.88 (95% CI 1.15-3.06), p-value=0.062 • D01AE: Other antifungals for topical use: aHR=0.82 (95% CI 0.12-5.85), p-value=0.935 • D02AC: Soft paraffin and fat products: aHR=33.38 (95% CI 4.67-238.46), p-value=0.008 • D04AB: Anesthetics for topical use: aHR=15.82 (95% CI 2.22-112.87), p-value=0.040 • D06AX: Other antibiotics for topical use: aHR=2.13 (95% CI 1.01-4.51), p-value=0.176 • D06BB: Antivirals: aHR=1.20 (95% CI 0.30-4.81), p-value=0.917 • D07AA: Corticosteroids, weak (group i): aHR=2.90 (95% CI 1.08-7.78), p-value=0.143 • D07AB: Corticosteroids, moderately potent (group ii): aHR=0.75 (95% CI 0.31-1.82), p-value=0.661 • D07AC: Corticosteroids, potent (group iii): aHR=1.47 (95% CI 0.70-3.12), p-value=0.530 • D07BB: Corticosteroids, moderately potent, combination with antiseptic: aHR=3.17 (95% CI 0.79-12.75), p-value=0.299 • D07BC: Corticosteroids, potent, combination with antiseptic: aHR=2.74 (95% CI 0.38-19.56), p-value=0.530	

Study details	Participants	Factors and results	Comments
		• D07CB: Corticosteroids, moderately potent, combination with antibiotic: aHR=6.40 (95% CI 1.59-25.74), p-value=0.054 • D07CC: Corticosteroids, potent, combination with antibiotic: aHR=2.20 (95% CI 0.70-6.86), p-value=0.430 • D10AF: Anti-infectives for treatment of acne: aHR=2.23 (95% CI 0.72-6.98), p-value=0.399 • G01AF: Imidazole derivatives: aHR:1.73 (1.18-2.54), p-value=0.040 • G03AA: Progestogens and estrogens, fixed combinations: aHR=0.91 (95% CI 0.23-3.66), p-value=0.939 • G03AC: Progestogens: aHR=2.06 (95% CI 0.28-14.99), p-value=0.614 • G03CA:Natural and semisynthetic oestrogens, plain: aHR: 3.34 (95% CI 1.48-7.55), p-value=0.035 • G03DA: Pregnen: aHR= 3.22 (95% CI 1.97-5.52), p-value=0.001 • G03GA: Gonadotrophins: aHR=1.39 (95% CI 0.69-2.82), p-value=0.537 • G03GB: Ovulation stimulants, synthetic: 0.88 (95% CI 0.12-6.29), p-value=0.939 • H01CC: Anti gonadotrophin releasing hormones: aHR=2.80 (95% CI 0.69-11.31), p-value=0.371 • H02AB: Glucocorticoids: aHR=2.14 (95% CI 0.68-6.68), p-value=0.419 • H03AA: Thyroid hormones: aHR=1.52 (95% CI 0.41-5.61), p-value=0.661 • H03BB: Sulphur-containing imidazole derivatives: aHR=3.15 (95% CI 0.44-22.49), p-value=0.472 • H04AA: Glycogenolytic hormones: aHR=2.54 (95% CI 0.35-18.16), p-value=0.537 • J01CA: Penicillins with extended spectrum: aHR=1.71 (95% CI 1.29-2.27), p-value=0.005	

Study details	Participants	Factors and results	Comments
		• J01CE: Beta-lactamase sensitive pencillins: aHR=1.47 (95% CI 1.06-2.04), p-value= 0.103 • J01CF: Beta-lactamase resistant penicillins: aHR=2.31 (95% CI 0.86-6.21), p-value=0.292 • J01EB: Short-acting sulphonamides: aHR=1.36 (95% CI 0.87-2.13), p-value=0.403 • J01FA: Macrolides: aHR= 2.24 (95% CI 1.28-3.92), p-value=0.039 • J01XE: Nitrofuran derivatives: aHR=1.61 (95% CI 0.66-3.90), p-value=0.516 • J02AC: Triazole derivatives: aHR=1.13 (95% CI 0.36-3.53), p-value=0.932 • J05AB: Nucleosides and nucleotides excluding reverse transcriptase inhibitors: aHR=2.29 (95% CI 0.85-6.14), p-value=0.296 • J05AH: Neuraminidase inhibitors: aHR=1.51 (0.21-10.77), p-value=0.800 • J06BA: Immunoglobulins, normal human: aHR=5.95 (0.84-42.43), p-value=0.249 • J07BM: Papillomavirus vaccines: aHR=18.42 (95% CI 2.57-132.05), p-value= 0.035 • L04AX: Other immunosuppressants: aHR=4.85 (95% CI 0.68-34.72), p-value=0.310 • M01AB: Acetic acid derivatives and related substances: aHR=1.62 (95% CI 0.52-5.04), p-value=0.576 • M01AE: Propionic acid derivatives: aHR=1.24 (95% CI 0.55-2.79), p-value=0.730 • M01AX: Other anti-inflammatory/ anti-rheumatic agents, mom-steroids: aHR=12.78 (95% CI 1.79-91.12), p-value=0.060 • M02AA: Anti-inflammatory preparations, non-steroids for topical use: aHR=3.73 (95% CI 0.53-26.65), p-value=0.419	

Study details	Participants	Factors and results	Comments
		• N02AA: Natural opium alkaloids: aHR=1.73 (95% CI 0.42-6.95), p-value=0.588 • N02AX: Other opioids: aHR=1.71 (95% CI 0.42-6.89), p-value=0.595 • N02BE: Anilides: aHR=1.84 (95% CI 0.59-5.75), p-value=0.516 • N02CC: Selective 5HT(1)-receptor agonists: aHR=0.89 (95% CI 0.13-6.37), p-value=0.939 • N03AE: Benzodiazepine derivatives: aHR=8.62 (95% CI 1.20-61.61, p-value=0.137 • N05AF: Carboxamide derivatives: aHR=8.76 (95% CI 1.23-62.49), p-value=0.137 • N05BA: Benzodiazepine derivatives: aHR=4.52 (95% CI 1.86-11.00), p-value=0.012 • N05CF: Benzodiazepine related drugs: aHR=2.52 (95% CI 1.13-11.01), p-value=0.137 • N06AB: Selective serotonin reuptake inhibitors: aHR=1.52 (95% CI 0.78-2.97), p-value=0.429 • N06BA: Centrally acting sympathomimetics: aHR=6.34 (95% CI 0.88-45.47), p-value=0.228 • N07BC: Drugs used in opioid dependence: aHR=8.25 (95% CI 1.13-6.39), p-value=0.939 • P01AB: Nitroimidazole derivatives: aHR=1.63 (95% CI 0.52-5.07), p-value=0.575 • P02CA: Benzimidazole derivatives: aHR=0.89 (95% CI 0.13-6.39), p-value=0.939 • P02CX: Other antiematodals: aHR=3.14 (95% CI 0.78-12.67), p-value=0.302 • R01AC: Antiallergic agents, excluding corticosteroids: aHR=1.20 (95% CI 0.17-8.58), p-value=0.935	

Study details	Participants	Factors and results	Comments
		• R01AD: Corticosteroids: aHR=1.34 (95% CI 0.75-2.38), p-value=0.537 • R03AC: Selective beta-2-adrenoceptor agonists: aHR=2.23 (95% CI 1.33-3.76), p-value=0.029 • R03AK: Adrenergics and other drugs for obstructive airway diseases: aHR=1.66 (95% CI 0.53-5.18), p-value=0.565 • R03BA: Glucocorticoids: aHR=1.67 (95% CI 0.74-3.74), p-value=0.439 • R03CC: Selective beta-2-adrenoreceptor agonists: aHR=3.59 (95% CI 0.50-25.59), p-values= 0.426 • R05DA: Opium alkaloids and derivatives: aHR=2.79 (95% CI 1.31-5.93), p-value=0.049 • R05FA: Opium derivatives and expectorants: aHR=2.00 (95% CI 0.50-8.05), p-value=0.537 • R06AD: Phenothiazine derivatives: aHR=2.36 (95% CI 0.33-16.85), p-value=0.570 • R06AE: Piperazine derivatives: aHR=1.19 (95% CI 0.53-2.68), p-value=0.799 • R06AX: Other antihistamines for systemic use: aHR=1.15 (95% CI 0.43-3.09), p-value=0.903 • S01AA: Antibiotics: aHR=0.55 (95% CI 0.21-1.48), p-value=0.449 • S01AX: Other anti-infectives: aHR=5.86 (95% CI 0.82-41.8), p-value=0.250 • S01BA: Corticosteroids, plain: aHR=2.51 (95% CI 0.35-17.9), p-value=0.537 • S01GA: Sympathomimetics used as decongestants: aHR=1.04 (95% CI 0.26-4.18), p-value=0.975 • S01GX: Other anti-allergics: aHR=0.98 (95% CI 0.32-3.07), p-value=0.988 • S02CA: Corticosteroids and anti-infectives in combination: aHR=1.01 (95% CI 0.14-7.22), p-value=0.989	

Study details	Participants	Factors and results	Comments
		• S03CA: Corticosteroids and anti-infectives in combination: aHR=1.92 (95% CI 0.48-7.70), p-value=0.537 Sensitivity analysis for the association of medications with VTE including all pregnancies for each woman during the period produced similar results although some ATC5-groups lost or gained significance.	
Full citation Kane, E. V., Calderwood, C., Dobbie, R., Morris, C., Roman, E., Greer, I. A., A population-based study of venous thrombosis in pregnancy in Scotland 1980-2005, European Journal of Obstetrics Gynecology and Reproductive Biology, 169, 223-229, 2013 **Ref Id** 652649 **Country/ies where the study was carried out** Scotland **Study type** Population-based retrospective cohort study **Study dates** 1980-2005 **Consecutive recruitment** Yes	**Cases** 2006 deliveries with VTE of any kind in pregnancy and postpartum (1287 antenatal DVT, 498 postnatal DVT, 290 PE. Note some women had VTE at multiple time points or unclassified categories therefore numbers do not add up to 2,006)**Diagnostic criteria** ICD-9 codes **Controls** 1,473,295 deliveries without VTE deliveries **Inclusion criteria** • Deliveries in Scotland to women aged 13–48 years from 1980 to 2005 from the register of Scottish Morbidity record (SMR2)	**Factors** VTE was defined as DVT or PE according ICD-9 codes. • **Risk factors assessed include**: parity, previous VTE, antenatal haemorrhage, preeclampsia, hypertension, and deprivation as well as maternal age at delivery and year of delivery. • Data for potential risk factors were obtained from the register. Deprivation was based on Carstairs score; an area-based measure of socioeconomic status calculated using 1991 Scottish census data. No other definition was provided **Adjusted relative risk/odds ratio** Total number of VTE events: n=2006; Antenatal DVT: n=1287; Postnatal DVT n=498; PTE: n=290 • Note: 79 deliveries had antenatal and postnatal DVT; 15 deliveries had DVT and PTE, 12 deliveries had postnatal DVT and PTE, 1 delivery had antenatal and postnatal DVT as well as PTE; type of VTE for 39 deliveries was unknown.	**Limitations** **QUIPS checklist** Study participation: Low risk (no area of concerns for this domain) Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (partial definition of factors, unsure if method and setting of measurement is the same for all participants, may likely introduce substantive bias) Outcome measurement: High risk (VTE not identified objectively, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantial bias) Study confounding: High risk (results adjusted for 10 covariates; but did not adjust for BMI, smoking, immobilisation, multiple pregnancies, and thromboprophylaxis, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (Partial concerns about the description of the regression model, unlikely to introduce substantial bias) **Overall quality: Low** **Other information**

Study details	Participants	Factors and results	Comments
Funding • None reported	**Exclusion criteria** • Discrepancies in the data of 1 health board (n=82,712 deliveries) **Statistical method** • The incidence of VTE in pregnancy and postpartum adjusted for age and year was calculated relative to the total number of hospital deliveries. • Age-specific incidence rates (IR) were calculated by single year. • Three year moving averages of IR was plotted for age and time trend. • Incidence rate ratios (IRR) and 95% confidence intervals (CI) were estimated using Poisson regression. **Demographics** **Total number of deliveries:** N=1,475,301 **Age** Total Mean (SD): Total cohort: 27.2 (5.55) • <25: n=493,435 • 25-34: n=831,043	**Adjusted IRR for the association between assessed risk factors and antenatal DVT reported with 95% CI** (result adjusted for age at delivery, year of delivery, deprivation, parity, hypertension, previous VTE, haemorrhage, preeclampsia, postnatal DVT and mode of delivery) **Age (mean, SD):** Antenatal DVT= 27.6 (5.84) (aIRR=1.06; 95%CI: 1.01-1.11) • <25: total deliveries:n= 493,036; Antenatal DVT= 399 (aIRR=1.0 as reference) • 25-34: total deliveries: n= 830,337; Antenatal DVT= 706 (aIRR=1.06; 95%CI: 0.93-1.20) • ≥35: total deliveries: n= 150,823; Antenatal DVT= 182 (aIRR=1.33; 95%CI: 1.10-1.60) **Year of delivery**: (aIRR=1.09; 95%CI: 1.05-1.14) • 1980-1985: total deliveries: n=371,958; Antenatal DVT= 309 (aIRR=1.0 as Reference) • 1986-1990: total deliveries: n=305,967; Antenatal DVT= 246 (aIRR=0.97; 95%CI: 0.82-1.15) • 1991-1995: total deliveries: n=296,038; Antenatal DVT= 214 (aIRR=0.86; 95%CI: 0.72-1.03) • 1996-2000: total deliveries: n=262,711; Antenatal DVT= 222 (aIRR=1.00; 95%CI: 0.84-1.20) • 2001-2005: total deliveries: n=238,627; Antenatal DVT= 296 (aIRR=1.49; 95%CI: 1.26-1.76)	• Note: Association between risk factors and postnatal DVT and PTE were reported but data not extracted. PTE data was not extracted because it was not clear at what time it occurred.

Study details	Participants	Factors and results	Comments
	• ≥35: n=150,823 **Deprivation: most affluent to least affluent** • 1st quintile: n=264,660 • 2nd quintile: n=267,301 • 3rd quintile: n=269,834 • 4th quintile: n=290,056 • 5th quintile: n=345,362 • Not recorded: n=38,538 **Parity** • 0: n=725,228 • 1-2: n=667,418 • ≥3: n=82,648 **Previous VTE** • No: n=1,462,434 • Yes: n=12,867 **Hypertension** • No: n=1,298,755 • Yes: n=176,546 **Pre-eclampsia** • No: n= 1,403,448 • Yes: n= 71,853 **Antenatal haemorrhage**	**Deprivation: most affluent to least affluent** • 1st quintile: total deliveries: n= 264,660; Antenatal DVT= 234 (aIRR=1.0 as reference (most affluent)) • 2nd quintile: total deliveries: n= 267, 301; Antenatal DVT= 223 (aIRR=0.98; 95%CI: 0.81-1.17) • 3rd quintile: total deliveries: n= 269,384; Antenatal DVT= 202 (aIRR=0.89; 95%CI: 0.74-1.07) • 4th quintile: total deliveries: n= 290,059; Antenatal DVT= 247 (aIRR=1.02; 95%CI: 0.85-1.22) • 5th quintile: total deliveries: n= 345,362; Antenatal DVT= 354 (aIRR=1.26; 95%CI: 1.06-1.49) • Missing: total deliveries: n= 38,538; Antenatal DVT= 27 (aIRR=0.90; 95%CI: 0.60-1.35) **Parity** • 0: total deliveries: n= 725,228; Antenatal DVT= 650 (aIRR=1.00 as reference) • 1-2: total deliveries: n= 667,418; Antenatal DVT= 524 (aIRR=0.80; 95%CI: 0.71-0.90) • ≥3: total deliveries: n= 82,648; Antenatal DVT= 113 (aIRR=1.19; 95%CI: 0.96-1.46) **Previous VTE** • No: control: total deliveries: n= 1,462,434; Antenatal DVT= 1,207 (aIRR=1.0 as reference)	

Study details	Participants	Factors and results	Comments
	• No: n= 1,338,579 • Yes: n= 86,722 N.B: 7 deliveries had no information on parity	• Yes: control: total deliveries: n= 12,867; Antenatal DVT= 80 (aIRR=7.97; 95%CI: 6.30-10.10) **Hypertension** • No: total deliveries: n= 1,298,755; Antenatal DVT= 1,110 (aIRR=1.0 as reference) • Yes: total deliveries: n= 176,546; Antenatal DVT= 177 (aIRR=1.18; 95%CI: 0.96-1.44) **Pre-eclampsia** • No: total deliveries: n= 1,403,448; Antenatal DVT= 1,216 (aIRR=1.0 as reference) • Yes: total deliveries: n= 71,853; Antenatal DVT= 71 (aIRR=1.03; 95%CI: 0.76-1.39) **Antenatal haemorrhage** • No: total deliveries: n= 1,338,579; Antenatal DVT= 1,186 (aIRR=1.0 as reference) • Yes: total deliveries: n= 86,722; Antenatal DVT= 101 (aIRR=1.34; 95%CI: 1.09-1.64).	
Full citation Larsen, T. B., Johnsen, S. P., Gislum, M., Moller, C. A., Larsen, H., Sorensen, H. T., ABO blood groups and risk of venous thromboembolism	**Cases** 129 women with VTE **Diagnostic criteria**	**Factors** Definition of VTE: DVT was considered verified when both typical clinical symptoms and the venography or ultrasonography findings (stated in the medical records) were in agreement with DVT. PE was defined as clinical symptoms	**Limitations** **QUIPS checklist** Study participation: Low risk (only hospitalised cases included, power calculation not performed, unlikely to introduce substantial bias)

Study details	Participants	Factors and results	Comments
during pregnancy and the puerperium. A population-based, nested case-control study, Journal of Thrombosis & HaemostasisJ Thromb Haemost, 3, 300-4, 2005 **Ref Id** 998171 **Country/ies where the study was carried out** Denmark **Study type** Nested case-control study **Study dates** 01/01/1980-31/12/2001 **Consecutive recruitment** yes **Funding** • Study supported by Western Danish Research Forum for Health Sciences, and the Health Insurance Foundation but it was unclear if authors received funding from the organisations.	ICD-8 from 1977 to 1993 and ICD-10 afterwards **Controls** 258 women with no VTE **Inclusion criteria** • Women registered with a verified VTE diagnosis during pregnancy or puerperium from the regional Hospital Discharge Register of North Jutland County. • Medical records of possible cases with verified diagnosis. • All births registered with an incident diagnosis of DVT or PE • Resident in North Jutland County • Two controls selected for each case using hospital discharge registry. Controls were resident of the Northland Jutland County, matched on date of delivery for the case without previous VTE **Exclusion criteria** • Previous history of VTE • VTE patients from 1977 to 1979	supported by findings from a pulmonary angiography, a ventilation-perfusion lung scan, a computed tomography, or an autopsy. All cases with an uncertain diagnosis based on the available information were discussed until a consensus was reached. • Risk factors assessed are Blood Groups • Data about blood groups were obtained from blood transfusion sheets included in the medical records. **Adjusted relative risk/odds ratio** • Women with VTE=129; control without VTE=258 (61 VTE events during pregnancy; 68 VTE events during postpartum) **Adjusted odds ratio (aOR) of the association between Blood groups and VTE was assessed during pregnancy with 95% confidence interval (CI)** (Adjusted for age of mother, smoking, parity, clomiphene citrate stimulation, history of diabetes mellitus and BMI): **Blood Groups** • O: aOR=1.0 as reference • A: aOR=3.9 (95% CI: 1.5-9.7) • B: aOR=1.5 (95% CI: 0.4-5.5) • AB: aOR=2.2 (95% CI: 0.4-12.5)	Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (smoking status was recorded only at first antenatal visit, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Outcome measurement: Moderate risk (study used ICD- 8 and 10 codes to identify DVT or PE and VTE but diagnosis of patients was objective, partial concerns for the confirmation of the cases with uncertain record, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Study confounding: Low risk (results adjusted for 6 covariates, unsure if method and setting of measurement is the same for all participants, unlikely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concerns for this domain) **Overall quality: Acceptable** **Other information** Adjusted odds ratio (aOR) for VTE and Blood groups during postpartum was reported but data was not extracted

Study details	Participants	Factors and results	Comments
	• Patients with a verified diagnosis of superficial thrombophlebitis **Statistical method** • Adjusted odds ratios (ORs) for possible confounding factors estimated by logistic regression. • Separate analyses carried out for VTE events during pregnancy and postpartum, respectively, and for DVT and PE, respectively. • 95% CIs estimated for all analyses. • No power calculation performed **Demographics** **Total population** Cohort of N=71,729 women with 124,833 deliveries with 123,007 singleton deliveries **Blood Groups (%)** • O: with VTE (26.4); without VTE (39.5) • A: with VTE (54.3); without VTE (39.9) • B: with VTE (10.9); without VTE (14.0)		

Study details	Participants	Factors and results	Comments
	• AB: with VTE (6.2); without VTE (5.4) • Missing: with VTE (2.3); without VTE (1.2). **Age** • Mean: with VTE=27.7 (min-max:16-40) • Mean: without VTE=27.8 (min-max:18-40) **Parity** • Primiparous (%): with VTE =45.1; without VTE= 33.9 **Body mass index (BMI kg/m^2)** • Mean (min-max): with VTE =24.8 (17-57); without VTE= 22.8 (15-40) **Smoking (active smokers %)** • with VTE =50.5; without VTE=28.9 **Diabetes (%)** • with VTE=2.3; without VTE= 1.6 **IVF pregnancy (%)**		

Study details	Participants	Factors and results	Comments
	• with VTE=7.0; without VTE=1.2 N.B: data on all variable available for 84.5% of the population		
Full citation Larsen, T. B., Sorensen, H. T., Gislum, M., Johnsen, S. P., Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study, Thrombosis Research, 120, 505-9, 2007 **Ref Id** 562461 **Country/ies where the study was carried out** Denmark **Study type** Population-based nested case-control study **Study dates** 01/011980-31/12/2001 **Consecutive recruitment** Yes	**Cases** 129 women with VTE **Diagnostic criteria** ICD-8 from 1977 to 1993 and ICD-10 afterwards **Controls** 258 women without VTE **Inclusion criteria** • Women registered with a verified VTE diagnosis during pregnancy or puerperium from the regional Hospital Discharge Register of North Jutland County. • Medical records of possible cases with verified diagnosis. • All births registered with an incident diagnosis of DVT or PE. • Resident in North Jutland County. • Two controls selected for each case using hospital discharge registry. Controls were	**Factors** Definition of VTE: DVT was considered verified when both typical clinical symptoms and the venography or ultrasonography findings (stated in the medical records) were in agreement with DVT. PE was defined as clinical symptoms supported by findings from a pulmonary angiography, a ventilation-perfusion lung scan, a computed tomography, or an autopsy. All cases with an uncertain diagnosis based on the available information were discussed until a consensus was reached. • Risk factors assessed are: BMI and Smoking Definition of risk factors: • Smoking status at first antenatal visit was defined as current smoker or non-smoker. • Body mass index (BMI) at first antenatal visit was calculated as weight in kilograms divided by height in meters squared. • Overweight was defined as a BMI between 25 and 30 kg/m2, and obesity was defined as a BMI >30 kg/m^2.	**Limitations** **QUIPS checklist** Study participation: Low risk (hospitalised cases only included, power calculation not performed, unlikely to introduce substantial bias) Study attrition: Low risk (attrition not an issue given study based on register) Prognostic factor measurement: Moderate risk (smoking status was recorded at first antenatal visit, unsure if method and setting is the same for all participant, may likely introduce substantial bias) Outcome measurement: Moderate risk (study used ICD- 8 and 10 codes to identify DVT or PE and VTE but VTE was diagnosed objectively, partial concern for the confirmation of diagnosis of women with uncertain records, unsure method and setting of measurement is the same for all participants, may likely introduce substantial bias) Study confounding: Low risk (results adjusted for 6 covariates, unlikely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concern for this domain) **Overall quality: Acceptable** **Other information**

Study details	Participants	Factors and results	Comments
Funding • Study supported by Western Danish Research Forum for Health Sciences, and the Health Insurance Foundation, but unclear if authors received funding from the organisations.	resident of the Northland Jutland County, matched on date of delivery for the case without previous VTE. **Exclusion criteria** • Previous history of VTE • VTE patients from 1977 to 1979 • Patients with a verified diagnosis of superficial thrombophlebitis **Statistical method** • Crude and adjusted odds ratio (aORs) as measures of relative risk with 95% confidence intervals (CI) was estimated with logistic regression. • Possible interaction between smoking and obesity was examined both by stratified analyses and by including interaction terms in the logistic regression analyses. • No power calculation performed **Demographics**	**Adjusted relative risk/odds ratio** Women with VTE=129; control without VTE=258 (61 VTE events during pregnancy; 68 VTE events during postpartum). Adjusted odds ratio (aOR) of the association between Obesity and Smoking and VTE was assessed during pregnancy (adjustment controlled for age of mother, smoking, parity, clomiphene, citrate stimulation, diabetes mellitus and BMI): **Body mass index (BMI kg/m^2)** • <25: cases: n=26; control: n=164; aOR=1.0 as reference • 25-30: cases: n=9; control: n=36; aOR=1.6 (95% CI: 0.6-4.4) • >30: cases: n=12; control: n=10; aOR=9.7 (95% CI: 3.1-30.8) **Smoking** • Non-smokers: cases: n=16; control: n=151; aOR=1.0 as reference • Current smokers: cases: n=31; control: n=59; aOR=5.7 (95% CI: 2.5-13.2)	Adjusted odds ratio (aOR) for VTE and BMI and smoking during postpartum was reported but data was not extracted

Study details	Participants	Factors and results	Comments
	Total population Cohort of n=71,729 women **Age** • Mean: with VTE=27.7 (min-max:16-40) • Mean: without VTE=27.8 (min-max:18-40) **Parity** • Primiparous (%): with VTE=45.1; without VTE=33.9 **Body mass index (BMI kg/m^2)** • mean: with VTE= 24.8 (min=17-max=57); without VTE= 22.8 (min=15-max=40) **Current smokers (%)** • with VTE= 50.5; without VTE=28.9 **Diabetes (%)** • with VTE=2.3%; without VTE=1.6 **IVF pregnancy (%)** • with VTE=7.0; without VTE=1.2		

Study details	Participants	Factors and results	Comments
Full citation Lindqvist, P., Dahlback, B., Marsal, K., Thrombotic risk during pregnancy: A population study, Obstetrics and Gynecology, 94, 595-599, 1999 **Ref Id** 997841 **Country/ies where the study was carried out** Sweden **Study type** Population-based retrospective cohort study **Study dates** 1990-1993 **Consecutive recruitment** Yes **Funding** • Funded by University Hospital in Malmo research fund	**Cases** 608 women with VTE either antenatally (N=308) or postnatally (N=300) **Diagnostic criteria** ICD-9 **Controls** 114,940 women without VTE **Inclusion criteria** • All deliveries with hospitalisation from the national birth register. • Cases were all women with pregnancy-related thrombosis during the 1990–1993 based on ICD-9 codes • Control were all thrombosis-free pregnant women in the country during 1993 **Exclusion criteria** None stated **Statistical method**	**Factors** • Definition of Pregnancy-related thrombosis was DVT or PE according to ICD-9 codes related to pregnancy or the corresponding non-pregnant diagnosis codes. • Risk factors reported during pregnancy include: Maternal age; Parity; Smoking (No of cigarettes smoked daily); Multifetal pregnancy; and Preeclampsia. Risk factors are defined as: Smoking recorded at initial antenatal appointment classified in terms of daily cigarette consumption [≥10 (heavy smokers); 1–9 (moderate smokers); or 0 (non-smokers or not regular smokers). Preeclampsia defined as the combination of blood pressure >139/89 mmHg and albuminuria (at least 0.3 g/L). Parity classified as para 0, para 1, para 2, or at least para 3, para 1 chosen as the reference class because bivariate analysis showed it to be associated with the lowest odds ratio (OR) for thrombosis. Maternal age first classified according to five age groups (under 20, 20–24, 25–29, 30–34, and at least 35 years of age), but because bivariate analysis found no significant differences in ORs among the 20–24-, 25–29-, and 30–34-year old age groups, in subsequent analysis they were combined as a 20–34-year-old age group and used as the reference class. **Adjusted relative risk/odds ratio**	**Limitations** **QUIPS checklist** Study participation: Low risk (hospitalised cases only included unlikely introduce substantial bias) Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (some data on smoking were missing, smoking status was recorded at first antenatal appointment only, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Outcome measurement: High risk (VTE not identified objectively, unsure if method and setting is the same for all participants, very likely to introduce substantial bias). Study confounding: High risk (results adjusted for 5 covariates; BMI and thromboprophylaxis not adjusted for, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concern for this domain) **Overall quality: Low** **Other information** Adjusted odds ratio (aOR) was reported for postpartum VTE risk factors but data not extracted

Study details	Participants	Factors and results	Comments
	• Bivariate and multiple logistic regression analyses used to determine relationship between the occurrence of VTE and the prognostic factors. • All explanatory variables were included in analysis of postpartum thrombosis, and all except caesarean delivery in analysis of antepartum thrombosis. • Relative risk was reported as odds ratio (OR) with 95% confidence interval (CI). • P<0.5 was considered statistically significant. • Only data on first pregnancies were included in logistic regression analysis **Demographics** Total population: N= 479,422 deliveries 608 women accounted for 625 VTE cases 44 women gave birth more than once: • 16 had recurrent VTE. • 1 had VTE 3 times during the 4 years. • 15 had 1 pregnancy-related VTE but a VTE pregnancy free 1993	Cases of VTE in pregnancy=308 (300 VTE events in postpartum); control without VTE=114,940 **Multivariate adjusted odds ratio (aOR) for the association between prognostic factors and VTE during pregnancy** (Adjusted for maternal age, parity, multiple pregnancy, smoking, and preeclampsia.) **Age (maternal)** • ≤19: with VTE=10; without VTE=2,817; aOR=1.00 (95% CI:0.5-1.9) • 20-34: with VTE=262; without VTE=97,904; aOR=1.00 as reference • ≥35: with VTE=36; without VTE=14,219; aOR=1.00 (95% CI:0.7-1.4) **Multiple pregnancy** • No: with VTE=299; without VTE=113,330; aOR=1.00 as reference • Yes: with VTE=9; without VTE=1,610; aOR=2.10 (95% CI:1.0-4.6) **Parity** • para 0: with VTE=178; without VTE=47,425; aOR=2.90 (95% CI:2.1-3.9) • para 1: with VTE=60; without VTE=40,734; aOR=1.00 as reference • para 2: with VTE=36; without VTE=18,113; aOR=1.30 (95% CI:0.8-2.0) • Para≥3: with VTE=34; without VTE=8,429; aOR=2.80 (95% CI:1.8-4.4)	

Study details	Participants	Factors and results	Comments
	• 13 women delivered twice during 1993 Complete information on weight and height available for less than 30% of the women. **Maternal age (classification 1)** • ≤19: VTE case: n= 26; control n=2,817 • 20-24: VTE case: n= 125; control n=23,006 • 25-29: VTE case: n= 216; control n=44,763 • 30-34: VTE case: n= 151; control n=30,135 • ≥35: VTE case: n= 90; control n=14,219 **Maternal age (classification 2)** • ≤19: VTE case: n= 26; control n=2,817 • 20-34: VTE case: n= 492; control n=97,904 • ≥35: VTE case: n= 90; control n=14,219 **Parity** • Para 0: VTE case: n= 304; control n=47,425 • Para 1: VTE case: n= 142; control n=40,734 • Para 2: VTE case: n= 93; control n=18,113 • ≥Para 3: VTE case: n= 69; control n=8,429	**Preeclampsia** • No: with VTE=301; without VTE=111,788; aOR=1.00 as reference • Yes: with VTE=7; without VTE=3,152; aOR=0.80 (95% CI:0.4-1.6) **Smoking (no of cigarettes smoked daily)** • 0: with VTE=221; without VTE=87,408; aOR=1.00 as reference • 1-9: with VTE=39; without VTE=14,295; aOR=1.10 (95% CI:0.8-1.5) • ≥10: with VTE=28; without VTE=8,177; aOR=1.30 (95% CI:0.9-2.0)	

Study details	Participants	Factors and results	Comments
	• Missing: VTE case: n= 0; control n=239 **Smoking (no of cigarettes daily)** • 0: VTE case: n= 423; control n=87,408 • 1-9: VTE case: n= 80; control n=14,295 • ≥10: VTE case: n= 57; control n=8,177 • Missing: VTE case: n= 48; control n=5,060 **Multiple pregnancy** • No: VTE case: n= 593; control n=113,330 • Yes: VTE case: n= 15; control n=1,610 **Pre-eclampsia** • No: VTE case: n= 562; control n=111,788 • Yes: VTE case: n= 46; control n=3,152		
Full citation Rova, K., Passmark, H., Lindqvist, P. G., Venous thromboembolism in relation to in vitro fertilization: An approach to determining the	**Cases** 32 pregnancies with antenatal VTE in 19,194 pregnancies with IVF **Diagnostic criteria**	**Factors** VTE defined according to the ICD-10 codes as DVT, sinus thrombosis, and obstetric pulmonary embolism. Risk factors assessed include: IVF +/- OHSS; Maternal age; BMI (kg/m2); multiple	**Limitations** **QUIPS checklist** Study participation: Low risk (only hospitalised cases were included, but unlikely to introduce substantial bias)

Study details	Participants	Factors and results	Comments
incidence and increase in risk in successful cycles, Fertility and Sterility, 97, 95-100, 2012 **Ref Id** 998888 **Country/ies where the study was carried out** Sweden **Study type** Population-based retrospective cohort study **Study dates** 1999-2008 **Consecutive recruitment** Yes **Funding** • Study was supported with funding from the Karolinska Institute.	ICD-10 **Controls** 160 pregnancies with antenatal VTE in 935,338 pregnancies without IVF **Inclusion criteria** • All deliveries in Sweden from 1999 to 2008 registered in the Medical Birth Registry. • Women giving birth with a diagnosis of VTE in relation to pregnancy and during the first 42 postpartum days. • Women with VTE as a complication of successful IVF pregnancies from the Swedish IVF registry were cases. • Women who gave birth without an OHSS diagnosis code not included in the IVF registry were included as cases. • Women with OHSS not giving birth during the period of the study. • Controls were women without IVF. **Exclusion criteria** • None stated **Statistical method**	pregnancy; and Smoking. Only IVF +/- OHSS, Maternal age, BMI assessed in multivariable analysis <u>Definition for risk factors:</u> • Parity classified as no prior delivery, one or two prior deliveries (reference), or more than two prior deliveries. • Multiple pregnancies were pregnancies with more than one foetus. • Smoking was dichotomized into non-smoking and smoking in early pregnancy (daily smokers). • BMI was not defined. • Ovarian hyperstimulation syndrome defined as requiring hospitalisation as a result of OHSS • IVF was dichotomised into Fresh IVF/ICSI(intracytoplasmic sperm injection) and frozen embryo replacement (FER) cycles **Adjusted relative risk/odds ratio** **<u>Total VTE during pregnancy</u>** • Trimester 1: With IVF=32; without IVF=160 • Trimester 2: With IVF=5; without IVF=164 • Trimester 3: With IVF=13; without IVF=555 • Unknown trimester: With IVF=1; without IVF=31 Total antepartum VTE: With IVF=51; without IVF=910; OR=2.7 (95%CI: 2.1-3.6)	Study attrition: Low risk (attrition not issue given study based on IVF register) Prognostic factor measurement: Moderate risk (BMI was not defined, partial concern about high number of BMI and OHSS data unknown, smoking recorded only at early pregnancy, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Outcome measurement: High risk (VTE not diagnosed objectively, unsure if method and setting of outcome measurement is the same for all participants, very likely to introduce substantial bias). Study confounding: High risk (thromboprophylaxis and smoking were not adjusted for, unsure if setting and measurement is the same for all participants, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concerns for this domain) **Overall quality: Low** **Other information** • Result presented some report for postpartum period but data not extracted

Study details	Participants	Factors and results	Comments
	• Bivariate and multiple logistic regression analyses used to determine the relationship between the occurrence of a thrombosis during the first trimester and prognostic factors. • Variables with p<0.1 in the bivariate analysis included in multivariate analysis. • A dummy variable used for the multivariate analysis to distinguish between IVF treatment with and without OHSS as a risk factor for VTE. • IVF pregnancies were also categorised as: fresh IVF cycles (with ovulation induction) and frozen embryo replacement (FER); no IVF as reference; IVF with OHSS, and FER • Relative risk determined as odds ratios (ORs) and 95% CIs • P<0.05 considered as statistically significant. • Power estimation reported. **Demographics** Total number of pregnancies N= 954,532 pregnancies • Maternal age: mean (SD): Pregnancies with IVF=33.5 (4.0); without IVF=30.0 (5.1)	• 7 cases of VTE among 1360 women with OHSS who did not give birth. But no data regarding whether they were conceived pregnancies. **VTE in first trimester** Multivariate analysis of adjusted odds ratio (OR) and 95% CI (Adjusted for: age; BMI; IVF; Fresh IVF not OHSS; Fresh IVF and OHSS; FER cycles). • Not IVF: with VTE=160; without VTE =935,178; aOR=1 as reference • Fresh IVF, not OHSS: with VTE=12; without VTE=14,520; aOR=4.7(95%CI: 2.6-8.4) • Fresh IVF, and OHSS: with VTE=19; without VTE=1,113; aOR=101.0 (95%CI: 62.5-163.3) • FER cycles: VTE=1; without VTE=3,529; aOR=1.6 (95%CI: 0.2-11.3) *N.B: incidence of VTE after fresh IVF=0.9/1000.* **Maternal age** • <40: with VTE=178; without VTE=924,366 aOR=1 as reference • ≥40: with VTE=14; without VTE=29,974: aOR=2.10 (95% CI:1.3-3.7) **Body mass index (kg/m^2)** • <25: with VTE=84; without VTE=540,802: aOR=1 as reference	

Study details	Participants	Factors and results	Comments
	• Smokers: Pregnancies with IVF=786; without IVF=83,126 • Missing: Pregnancies with IVF=1,500; without IVF=57,123 • BMI (Kg/m^2): mean (SD): Pregnancies with IVF=21.4 (9.1); without IVF=21.7 (8.9) • Multiple pregnancies: Pregnancies with IVF=2,426; without IVF=11819 • OHSS: Pregnancies with IVF=1,291. **Maternal age** • <20: Pregnancies with IVF=3; without IVF=16,577 • 20≤30: Pregnancies with IVF=3,115; without IVF=412,518 • 30≤40: Pregnancies with IVF=14,825; without IVF=477,506 • >40: Pregnancies with IVF=1,251; without IVF=28,737 **Parity** • Nulliparous: Pregnancies with IVF=13,131; without IVF=409,716 • 1 delivery: Pregnancies with IVF=4,853; without IVF=339,452 • 2 deliveries: Pregnancies with IVF=932; without IVF=129,444	• ≥25-<30: with VTE=40; without VTE=209,723: aOR=1.2 (95% CI:0.8-1.8) • ≥30: with VTE=46; without VTE=92,689: aOR=3.2 (95% CI:2.2-4.6) • Unknown: with VTE=22; without VTE=111,126: aOR=1.3 (95% CI:0.8-2.1)	

Study details	Participants	Factors and results	Comments
	• >2 deliveries: Pregnancies with IVF=27; without IVF=56,726		
Full citation Scheres, L. J. J., Lijfering, W. M., Groenewegen, N. F. M., Koole, S., De Groot, C. J. M., Middeldorp, S., Cannegieter, S. C., Hypertensive Complications of Pregnancy and Risk of Venous Thromboembolism, Hypertension, 781-787, 2020 **Ref Id** 1250487 **Country/ies where the study was carried out** Netherlands **Study type** Population-based retrospective cohort study **Study dates** 1999 to 2012 **Consecutive recruitment** Yes **Funding**	**Cases** 710 first VTEs in first pregnancy or 3m postpartum **Diagnostic criteria** Objective diagnosis **Controls** 1,919,208 without VTE **Inclusion criteria** Women from Dutch Perinatal Registery (covers 95-99% of deliveries in Netherlands) **Exclusion criteria** Women with pregnancy loss or missing date of birth in pregnancy, history of VTE, missing data on values need for follow-up calculation (0.6%) **Statistical method** Cox proportional hazard ratios were calculated per risk factor. Analyses were adjusted for number of	**Factors** Hypertension of pregnancy (at least 1 occasion diastolic BP of 90mmHg or higher, without proteniuria of ≥300mg per 24 hours). Note - no differentation between pre-existing and gestational hypertension. Preeclampsia as above but with proteinuria. DBP was chosen as data was complete in registry (unlike for systolic BP). **Adjusted relative risk/odds ratio** Information on VTE captured from linkage with anticoagulation clinics, in the Netherlands all VTE need objective imaging techniques for diagnosis and those treated with vitamin K antagonists are referred to anticoagulation clinics. Hypertension in pregnancy (vs uncomplicated pregnancy): HR 2.0 (95% CI 1.7 to 2.4) Preeclampsia (vs uncomplicated pregnancy): HR 7.8 (95% CI 5.4 to 11.3)	**Limitations** **QUIPS checklist** Study participation: Low risk (captures vast majority of birth in country). Study attrition: Low risk (missing data rate very low from registry data) Prognostic factor measurement: Low risk (unsure if method and setting is the same for all participants, unlikely to introduce substantial bias). Outcome measurement: High risk (VTE measured objectively, however defined by those attending clinic and therefore not including those who died or received non-clinic based treatment) Study confounding: High risk (only 3 confounders considered, important factors including smoking not adjusted for, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantial bias). Statistical analysis and reporting: Low risk (no areas of concern for this domain). **Overall quality: Low**

Study details	Participants	Factors and results	Comments
Charity (Dutch Heart Foundation)	pregnancies, age at start of follow-up, self-reported ancestry. **Demographics** **Age** Mean 29.5 (SD 5.0) for uncomplicated, 29.8 (SD 4.8) for hypertension, 29.3 (SD 5.0) for preeclampsia **Parity** Median 1 (IQR 1-2) for all 3 groups **Descent** Uncomplicated: 81% Dutch, 1.4% Hindustani, 17.6% other Hypertension: 89.3% Dutch, 1.0% Hindustani, 9.7% other Preeclampsia: 84.4% Dutch, 1.5% Hindustani, 14.1% other **Hypertension related** Hypertension in pregnancy 13.8% Preeclampsia 1.6%		
Full citation Simpson, E. L., Lawrenson, R. A., Nightingale, A. L., Farmer, R. D. T., Venous thromboembolism in pregnancy and the puerperium: Incidence and additional risk factors from a London perinatal database, British Journal of Obstetrics and Gynaecology, 108, 56-60, 2001 **Ref Id** 997971 **Country/ies where the study was carried out**	**Cases** 336 women with VTE **Diagnostic criteria** ICD-9(1988-1995); ICD-10(1995-1997) **Controls** 20,090 women without VTE **Inclusion criteria** • Pregnancy records of live birth or stillbirth at or after 24 completed weeks of gestation	**Factors** VTE was identified by ICD codes 9 and 10 including DVT and PE as well as other venous thrombosis not mentioned • Risk factors assessed include: Body mass index (BMI kg/m^2) at booking; Blood Group; and number of infants delivered. **Adjusted relative risk/odds ratio** Total of 336 cases of VTE (109 cases of antenatal VTE and 256 cases of postpartum VTE (including cases of both antenatal and postnatal	**Limitations** **QUIPS checklist** Study participation: Moderate risk (unmatched control included, inadequate baseline data reported, power calculation not performed, may likely introduce substantial bias) Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (20% of BMI data missing, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Outcome measurement: High risk (VTE not diagnosed objectively, other unspecified venous thrombosis was reported in result, unsure if method and

Study details	Participants	Factors and results	Comments
England **Study type** Retrospective nested case-control **Study dates** 1988-1997 **Consecutive recruitment** Yes **Funding** • None stated	from St Mary's Maternity Information System. • Cases were women with VTE in pregnancy and postpartum. • Control was an unmatched random 5% sample of women without a record of VTE **Exclusion criteria** • Pregnancies not resulting in a live birth or stillbirth, and any pregnancies that had incomplete records (usually due to the woman leaving the district prior to delivery). **Statistical method** • Forward and backward stepwise logistic regression analyses set to accept or remove variables at a significance of P<0.1. • Unconditional logistic regressions performed using all the relevant variables identified by the stepwise logistic regression models to obtain adjusted odds ratios. Unadjusted odds ratios were also calculated for each variable. • Eclampsia was not included in the multivariate analyses as it caused instability in the model.	events). Cases with both antenatal and postnatal events were included in the antenatal analysis. **Adjusted odds ratio (aOR) of the association between prognostic factors and VTE were assessed during pregnancy with 95% CI** (adjusted for number of infants this delivery, BMI, blood group): **Blood Group** • O: as reference • A: aOR=1.9 (95% CI:1.2-3.0) • B: aOR=1.6 (95% CI:0.9-2.9) • AB: aOR=1.6 (95% CI:0.6-4.1) • Missing: aOR=1.5 (95% CI:0.2-11.9) **Body mass index (BMI kg/m^2)** • <20: aOR=0.4 (95% CI:0.2-1.1) • 20-24.99: as reference • 25-29.99: aOR=1.2 (95% CI:0.8-2.0) • ≥30: =1.4 (95% CI:0.7-2.6) • Missing: aOR=1.0 (95% CI:0.5-1.7) **Number of infants delivered** • 1: aOR=1.0 as reference • ≥2 : aOR= 4.2 (95% CI: 1.8-9.7)	setting are the same for all participants, very likely to introduce substantial bias) Study confounding: High risk (results adjusted for 3 covariates; thromboprophylaxis and smoking not adjusted for, unsure if method and setting of measurement for all participants is the same, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concern for this domain) **Overall quality: Low** **Other information** N.B: Result presented report for postpartum VTE, data not extracted.

Study details	Participants	Factors and results	Comments
	• No power calculation reported. **Demographics** Total cohort N= 395,335 women. 23% of the women were non-Europeans **Age group** • <25: with VTE=72; total pregnancy=95,266 • 25-34: with VTE=207; total pregnancy=25,0534 • ≥35: with VTE=57; total pregnancy=49,529 **Preeclampsia** Record present in only 10 of the maternities. **Body Mass Index** Approximately 20% of the women on the database did not have sufficient data to calculate BMI		
Full citation Sultan, A. A., Tata, L. J., West, J., Fiaschi, L., Fleming, K. M., Nelson-Piercy, C., Grainge, M. J., Risk factors for first venous thromboembolism around pregnancy: A population-based cohort study from the United Kingdom, Blood, 121, 3953-3961, 2013 **Ref Id**	**Cases** 500 VTE events **Diagnostic criteria** Medical code by physicians=ICD codes **Controls** 375,654 pregnancies with no VTE **Inclusion criteria**	**Factors** Definition of VTEs include DVT or PE. VTE was based on a recorded medical code assigned by a physician and supplemented by evidence of anticoagulation prescription or a medical diagnosis indicating anticoagulant therapy within 90 days of the event date. **Definition of Risk factors:** Maternal age was considered as 15-24, 25-34, and 35-44 years.	**Limitations** **QUIPS checklist** Study participation: Low risk (no area of concerns for this domain) Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (BMI defined with pre-pregnancy record, unsure if method and setting is the same for all participants, may introduce substantial bias)

Study details	Participants	Factors and results	Comments
923238 **Country/ies where the study was carried out** UK **Study type** Population-based retrospective cohort study **Study dates** 01/1995-07/2009 **Consecutive recruitment** Yes **Funding** • Nelson-Piercy C. received payment from Leo Pharma for development of an educational slide kit about obstetric thromboprophylaxis.	• All incident pregnancies ending in live birth or stillbirth for women aged 15 to 44 years who contributed data to The Health Improvement Network (THIN) between January 1995 and July 2009 • Only women without a pre-pregnancy history of VTE were included. **Exclusion criteria** • Superficial VTE excluded • VTE cases and person time occurring within 1 month of the study start date were excluded. **Statistical method** • Absolute rates of VTE estimated per 100 000 person-years • Incident rate ratios (IRRs) of VTE associated with each risk factor estimated using Poisson regression models that were adjusted for confounders in model 1. • Other risk factors that were associated with increased risk for VTE included in the initial	BMI was latest measure recorded by the GP before the date of conception. Smoking status was defined as the latest measure recorded before delivery. ***Pregnancy related factors:*** These include: mode of delivery; birth outcome (live or stillborn child); length of gestation; multiple gestation; and number of previous births Women were defined as having gestational diabetes if they had a first record of diabetes during pregnancy and no prior prescriptions for oral hypoglycemics or insulin. Gestational hypertension was defined as a medical code indicating the condition during pregnancy or at least 3 readings of high blood pressure after the second trimester (systolic>140mmHg; diastolic> 90mmHg), with no antihypertensive treatment before pregnancy. Acute infections considered include urinary tract infection and acute respiratory tract infection (including pneumonia, acute bronchitis, chest infection, and influenza), during pregnancy. ***Existing relevant medical comorbidity*** was defined as: ever been diagnosed with cancer, systemic lupus erythematosus (SLE), or nephrotic syndrome or had recorded varicose veins, inflammatory bowel disease (IBD), or cardiac disease (including congestive cardiac disease, coronary artery disease, congenital heart disease, cardiomyopathy, angina, or myocardial infarction) during or before pregnancy. Pre-existing diabetes or pre-existing hypertension were also defined as conditions before conception.	Outcome measurement: High risk (VTE not diagnosed objectively, unsure if method and setting is the same for all patients, very likely to introduce substantial bias) Study confounding: Low risk (results adjusted for 8 covariates, unsure if method and setting of measurement are the same for all participants, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (no area of concerns for this domain) **Overall quality: Low** **Other information** • Gestational diabetes was dropped from model two due to colinearity

Study details	Participants	Factors and results	Comments
	antepartum and postpartum analyses (model 2). • Power estimation reported **Demographics** **Total population** N=376,154 pregnancies from 280,451 women • Live birth: n=375,002 • Still birth: n=1,152 **Pre-Pregnancy Body mass index (kg/m^2)** • Underweight (<18.5): n= 164,883 • Normal (18.5-24.9): n= 12,309 • Overweight (25-29.9): n= 66,068 • Obese (≥30): n= 31,101 • Missing: n=94,793 **Smoking** n=88,617 **Parity** 0: n= 213,697 1: n= 116,351 2: n= 33,819 ≥3: n= 12,287 **Multiple gestation** n= 6,251 **Eclampsia/preeclampsia** n= 1,897 **Gestational hypertension** n= 6,294 **Gestational diabetes**	**Adjusted relative risk/odds ratio** Total number of VTE events=500 (215 VTE cases in antepartum period; 285 cases occurred VTE in postpartum) period. **Model 1: Adjusted incident rate ratio (aIRR) of VTE in pregnancy associated with the assessed risk factors** (adjusted for age, parity, pre-pregnancy BMI, and smoking status when not stratified by them) **Maternal Age** • 15-24: VTE= 45; aIRR=0.87 (95%CI 0.61-1.24) • 25-34: VTE= 12; aIRR=1 as reference • 35-44: VTE= 50; aIRR=1.42 (95%CI 1.01-1.93) **Pre-Pregnancy Body mass index (kg/m^2)** • Underweight (<18.5): VTE= 3; aIRR=0.48 (95%CI 0.15-1.54) • Normal (18.5-24.9): VTE= 86; aIRR=1.00 • Overweight (25-29.9): VTE= 49; aIRR=1.41 (95%CI 0.99-2.00) • Obese (≥30): VTE= 30; aIRR=1.50 (95%CI 0.99-2.28) • No BMI recorded before conception: VTE= 47; aIRR=1.18 (95%CI 0.82-1.71)	

Study details	Participants	Factors and results	Comments
	n= 2,656 **Acute respiratory tract infection** n= 12,980 **urinary tract infection** n= 30,765 **Pre-existing diabetes** n= 4,022 **Pre-existing hypertension** n= 11,718 **Nephrotic syndrome** n= 214 **varicose veins** n= 8,373 **systemic lupus erythematous** n= 188 **cancer** n= 5,012 **inflammatory bowel disease** n= 1,472 **cardiac disease** n= 354	**Smoking** VTE= 55; aIRR=1.15 (95%CI 0.83-1.58) **Previous live births** • 0: VTE= 127; aIRR=1 as reference • 1: VTE= 60; aIRR=0.76 (95%CI 0.56-1.03) • 2: VTE= 19; aIRR=0.79 (95%CI 0.49-1.28) • ≥3: VTE= 9; aIRR=0.97 (95%CI 0.48-1.93) **Multiple gestation** VTE= 3; aIRR=0.83 (95%CI 0.26-2.61) **Gestational hypertension** VTE= 4; aIRR=1.01 (95%CI 0.37-2.76) **Gestational diabetes** VTE= 3; aIRR=1.71 (95%CI 0.54-5.41) **Acute respiratory tract infection** VTE= 13; aIRR=1.70 (95%CI 0.97-2.99) **Urinary tract infection** VTE= 31; aIRR=1.88 (95%CI 1.28-2.77) **Pre-existing diabetes** VTE= 8; aIRR=3.08 (95%CI 1.42-6.39) **Pre-existing hypertension** VTE= 7; aIRR=0.90 (95%CI 0.42-1.94) **Varicose veins** VTE= 13; aIRR=2.69 (95%CI 1.53-4.70) **Cancer** VTE= 6; aIRR=1.97 (95%CI 0.87-4.44) **Inflammatory bowel disease (IBD)** VTE= 3; aIRR=3.46 (95%CI 1.11-10.7) **Model 2: Adjusted incident rate ratio (aIRR) of VTE in pregnancy associated with the assessed risk factors** (adjusted for age, parity, pre-pregnancy BMI, pre-existing diabetes, IBD, varicose veins, acute systemic infection, and smoking status when not stratified by them): **Maternal Age**	

Study details	Participants	Factors and results	Comments
		• 15-24: VTE= 45; aIRR=0.89 (95%CI 0.62-1.27) • 25-34: VTE= 12; aIRR=1 as reference • 35-44: VTE= 50; aIRR=1.40 (95%CI 0.99-1.96) **Pre-Pregnancy Body mass index (kg/m^2)** • Underweight (<18.5): VTE= 3; aIRR=0.48 (95%CI 0.15-1.53) • Normal (18.5-24.9): VTE= 86; aIRR=1.00 • Overweight (25-29.9): VTE= 49; aIRR=1.40 (95%CI 0.98-2.00) • Obese (≥30): VTE= 30; aIRR=1.40 (0.90-2.16) • No BMI recorded before conception: VTE= 47; aIRR=1.16 (95%CI 0.85-1.69) **Smoking** VTE= 55; aIRR=1.16 (95%CI 0.84-1.60) **Previous live births** • 0: VTE= 127; aIRR=1 as reference • 1: VTE= 60; aIRR=0.72 (95%CI 0.53-0.98) • 2: VTE= 19; aIRR=0.71 (95%CI 0.43-1.16) • ≥3: VTE= 9; aIRR=0.89 (95%CI 0.45-1.78) **Multiple gestation** VTE= 3; aIRR=0.83 (95%CI 0.26-2.60) **Gestational hypertension** VTE= 4; aIRR=0.99 (95%CI 0.36-2.72) **Acute respiratory tract infection**	

Study details	Participants	Factors and results	Comments
		VTE= 13; aIRR=1.65 (95%CI 0.94-2.90) **Urinary tract infection** VTE= 31; aIRR=1.80 (95%CI 1.22-2.67) **Pre-existing diabetes** VTE= 8; aIRR=3.54 (95%CI 1.13-11.0) **Pre-existing hypertension** VTE= 7; aIRR=0.74 (95%CI 0.32-1.71) **Varicose veins** VTE= 13; aIRR=2.21 (95%CI 1.55-4.76) **Cancer** VTE= 6; aIRR=1.95 (95%CI 0.86-4.41) **Inflammatory bowel disease (IBD)** VTE= 3; aIRR=3.50 (95%CI 1.12-10.9)	
Full citation Sultan, A. A., West, J., Tata, L., Fleming, K., Nelson-Piercy, C., Grainge, M., Risk of first venous thromboembolism in pregnant women in hospital: Population based cohort study from England, BMJBmj, 347, 2013 **Ref Id** 999071 **Country/ies where the study was carried out** England **Study type** Population-based retrospective cohort study **Study dates**	**Cases** 176 pregnancies with VTE **Diagnostic criteria** Medical code **Controls** 245,485 pregnancies without VTE **Inclusion criteria** • All patients within a practice that consented to Clinical Practice Research Datalink (CPRD) (records of the patients were linked with hospital episode statistics (HES)) • Women aged 15-44 registered within CPRD-HES linked practices with no previous VTE	**Factors** VTE was defined by medical codes relating to the diagnosis of DVT or PE in HES or CPRD where there was evidence of anticoagulation within 90 days of diagnosis or if death occurred within 30 days of diagnosis. **Risk factors assessed** are hospital admission and after discharge which are defined as: • Admission was defined as the time between the date of admission and date of discharge; and post-discharge was up to 28 days after discharge date. • For admission: data on admission involving VTE and other than for delivery and not related to VTE lasting for one or more days were collected. **Other risk factors** • BMI: most recent recording before pregnancy	**Limitations** **QUIPS checklist** Study participation: Low risk (no area of concerns for this domain) Study attrition: Low risk (attrition not issue given study based on register) Prognostic factor measurement: Moderate risk (BMI defined with pre-pregnancy record, unsure if method and setting is the same for all participants, may likely introduce substantial bias) Outcome measurement: High risk (VTE was not diagnosed objectively, unsure if method and setting of outcome measurement is the same for all participants, very likely to introduce substantial bias) Study confounding: High risk (results adjusted for 8 covariates smoking was not adjusted for, unsure if method and setting of measurement is the same for all participants, very likely to introduce substantive bias)

Study details	Participants	Factors and results	Comments
1997-2010 **Consecutive recruitment** yes **Funding** • Nelson-Piercy C. received payment from Leo Pharma for development of an educational slide kit about obstetric thromboprophylaxis. • Sultan A was funded by a scholarship awarded by the Aga Khan Foundation. • West J was funded by a University of Nottingham senior clinical research fellowship, which also contributed to Sultan A funding.	who had at least 1 delivery resulting in live or still birth. **Exclusion criteria** • Practices from Northern Ireland, Wales, and Scotland were excluded • Pregnancies of women with previous VTE. **Statistical method** • Rates of VTE expressed per 100 000 person-years and 95% confidence intervals (CI). • Rate ratios estimated for risk factor for antepartum compared with baseline using a Poisson regression model, to determine which factors were associated with an increased risk of VTE. • Same process used to compare rates of VTE during admission and the 28 days after discharge with time outside hospital for antepartum. • Calculated incidence rate ratios were adjusted for age and calendar yeas as well as other risk factors found associated with increased risk of VTE	• Smoking status: latest recording before delivery **Pregnancy related factors:** include multiple gestation and complications such as: hyperemesis; antepartum haemorrhage • Gestational diabetes and gestational hypertension are defined as when the first medical code for the condition(or at least 3 readings of high blood pressure with systolic>140mmHg; and/or diastolic> 90mmHg recorded during pregnancy for gestational hypertension) took place during pregnancy with no previous medical codes or prescription for antidiabetic or antihypertensive drugs. • Women with previous records are classified as having pre-existing diabetes or hypertension. • Common infections include urinary tract infection and acute respiratory tract infection (including pneumonia, acute bronchitis, chest infection, and influenza) recorded during pregnancy. **Existing medical comorbidity** include varicose veins, inflammatory bowel disease (IBD), cardiac disease, and nephrotic syndrome	Statistical analysis and reporting: Low risk (no area of concerns for this domain) **Overall quality: Low**

Study details	Participants	Factors and results	Comments
	• Incidence rate ratio (IRR) comparing the rate of VTE during admission and after discharge to time outside hospital was adjusted for age and calendar year. • Absolute and relative rate was estimated for admission and after discharge restricting only to pregnancies in women admitted to hospital for 3 or more days with the presence of two or more risk factors including obesity (BMI >30) and any significant comorbidity • Sub-group analyses for antepartum combined the admission and post-discharge periods • Interactions between maternal age and admission was tested for by fitting an interaction term between them and conducting a likelihood ration test at the 5% level of significance. • Interaction between admission and BMI category was also tested for using the same procedure. **Demographics** Total population N=245,661 pregnancies from 206,785 women resulted in live or still birth. **Hospital admissions** • 0: n= 203,405 • 1: n= 30,784	**Adjusted relative risk/odds ratio** **Adjusted incident rate ratio (aIRR)** of the association between VTE and hospital admission and after discharge were reported with respective 95% confidence intervals (CI) **Model 1: adjusted incident rate of VTE by admission to hospital and after hospital stay (adjusting for maternal age and calendar year when not stratified by them)** **Overall event and aIRR during pregnancy** • outside hospital: VTE=150; aIRR=1.0 as reference • hospital admission: VTE=6; aIRR=18.2 (95% CI: 7.69-40.0) • after discharge: VTE=20; aIRR=7.08 (95% CI: 4.41-11.3) **Pregnancy not complicated by BMI>30 or major comorbidity** • outside hospital: VTE=109; aIRR=1.0 as reference • hospital admission: VTE=5; aIRR=22.0 (95% CI: 8.97-54.3) • after discharge: VTE=15; aIRR=7.56 (95% CI: 4.36-13.1) **Variation by duration of hospital stay (admission/after discharge)** • time outside hospital: VTE=150; aIRR=1 as reference	

Study details	Participants	Factors and results	Comments
	• 2: n= 7,470 • ≥3: n= 4,002 **Pre-pregnancy BMI (kg/m^2)** • Underweight (<18.5): n= 7,733 • Normal (18.5-24.9): n= 107,275 • Overweight (25-29.9): n= 45,132 • Obese (≥30): n= 28,701 • Missing: n= 56,820 **Smoking** • Non-smoker: n= 186,926 • smoker: n= 58,735 **Gestational diabetes:** n= 3,807 **Pre-existing diabetes:** n= 2,739 **Gestational hypertension:** n= 13,039 **Pre-existing hypertension:** n= 14,962 **Gestational acute systemic infection:** n= 32,668 **Hyperemesis:** n= 8,502 **Antepartum haemorrhage:** n= 11,614 **Multiple pregnancy:** n= 3,564 **Varicose veins:** n= 6,244 **Cardiac disease:** n= 2,471	• <3days: VTE=13; aIRR=5.85 (95% CI: 3.37-10.1) • ≥3days: VTE=13; aIRR=15.7 (95% CI: 8.71-28.5) **Time outside pregnancy** • outside hospital: VTE=326; aIRR=1.0 as reference • hospital admission: VTE=11; aIRR=66.2 95% CI: 36.3-120) • after discharge: VTE=35; aIRR=32.3 (95% CI: 22.8-45.8) **Model 2: adjusted incident rate of VTE by admission to hospital and after hospital stay** **Overall event and aIRR during pregnancy** • outside hospital: VTE=150; aIRR=1.0 as reference • hospital admission: VTE=6; aIRR=17.5 (95% CI: 7.69-40.0) • after discharge: VTE=20; aIRR=6.27 (95% CI: 3.74-10.5) **Variation by duration of hospital stay (admission/after discharge)** • time outside hospital: VTE=150; aIRR=1 as reference • <3days: VTE=13; aIRR=4.05 (95% CI: 2.23-7.38) • ≥3days: VTE=13; aIRR=12.2 (95% CI: 6.65-22.7) **Model 1: Rate of first antepartum VTE during hospital admission/after discharge stratified by trimester, age, and calendar year (adjusted**	

Study details	Participants	Factors and results	Comments
	<u>Inflammatory bowel disease:</u> n= 1,213 **Nephrotic syndrome:** n= 181	**for maternal age, calendar year when not stratified by them)** **aIRR of VTE by antepartum trimesters** • Time outside hospital: VTE=60; aIRR=1.00 as reference (Trimester 1 and 2) • Admission/after discharge: VTE=5; aIRR=7.61 (95% CI: 3.03-19.0) (Trimester 1 and 2) • Time outside hospital: VTE=90; aIRR=1.00 as reference (Trimester 3) • Admission/after discharge: VTE=21; aIRR=5.93 (95% CI: 3.64-9.65) (Trimester 3) **Variation by calendar year in admission/after discharge** • Time outside hospital: VTE=62; aIRR=1.00 as reference (1997-2003) • Admission/after discharge: VTE=8; aIRR=5.82 (95% CI: 2.76-12.2) (1997-2003) • Time outside hospital: VTE=88; aIRR=1.00 as reference (2004-2010) • Admission/after discharge: VTE=18; aIRR=10.1 (95% CI: 6.03-16.9) (2004-2010) **Variation by maternal age** • Time outside hospital: VTE=34; aIRR=1.00 as reference (15-24 years) • Admission/after discharge: VTE=4; aIRR=3.88 (95% CI: 1.37-10.9) (15-24 years)	

Study details	Participants	Factors and results	Comments
		• Time outside hospital: VTE=90; aIRR=1.00 as reference (25-34 years) • Admission/after discharge: VTE=13; aIRR=7.61 (95% CI: 4.24-13.6) (25-34 years) • Time outside hospital: VTE=26; aIRR=1.00 as reference (35-44 years) • Admission/after discharge: VTE=9; aIRR=19.6 (95% CI: 9.20-42.0) (35-34 years) **Variation by BMI** • Admission/after discharge: VTE=51; aIRR=1.00 (Normal BMI:18.5-24.9) • Time outside hospital: VTE=10; aIRR=6.24 (95%CI: 2.41-16.1) (Normal BMI:18.5-24.9) • Admission/after discharge: VTE=34; aIRR=1.00 (Overweight:25-29.9) • Time outside hospital: VTE=3; aIRR=10.3 (95%CI: 5.15-20.8) (Overweight:25-29.9) • Admission/after discharge: VTE=30; aIRR=1.00 (Obese:≥30) • Time outside hospital: VTE=5; aIRR=4.30 (95%CI: 1.30-14.1) (Obese:≥30) **Model 2: Rate of first antepartum VTE during hospital admission/after discharge stratified by trimester, age, and calendar year (adjusted for maternal age, calendar year, pre-pregnancy BMI, gestational infection, cardiac disease, varicose vein, gestational diabetes, and hyperemesis when not stratified by them) aIRR of VTE by antepartum trimesters**	

Study details	Participants	Factors and results	Comments
		• Time outside hospital: VTE=60; aIRR=1.00 as reference (Trimester 1 and 2) • Admission/after discharge: VTE=5; aIRR=8.43 (95% CI: 3.27-21.7) (Trimester 1 and 2) • Time outside hospital: VTE=90; aIRR=1.00 as reference (Trimester 3) • Admission/after discharge: VTE=21; aIRR=5.57 (95% CI: 3.32-9.34) (Trimester 3) **Variation by calendar year in admission/after discharge** • Time outside hospital: VTE=62; aIRR=1.00 as reference (1997-2003) • Admission/after discharge: VTE=8; aIRR=4.59 (95% CI: 2.08-10.1) (1997-2003) • Time outside hospital: VTE=88; aIRR=1.00 as reference (2004-2010) • Admission/after discharge: VTE=18; aIRR=8.51 (95% CI: 4.94-14.6) (2004-2010) **Variation by maternal age** • Time outside hospital: VTE=34; aIRR=1.00 as reference (15-24 years) • Admission/after discharge: VTE=4; aIRR=3.80 (95% CI: 1.25-11.5) (15-24 years) • Time outside hospital: VTE=90; aIRR=1.00 as reference (25-34 years)	

Study details	Participants	Factors and results	Comments
		• Admission/after discharge: VTE=13; aIRR=6.15 (95% CI: 3.24-11.7) (25-34 years) • Time outside hospital: VTE=26; aIRR=1.00 as reference (35-44 years) • Admission/after discharge: VTE=9; aIRR=21.7 (95% CI: 9.62-49.0) (35-34 years) **Variation by BMI** • Admission/after discharge: VTE=51; aIRR=1.00 (Normal BMI:18.5-24.9) • Time outside hospital: VTE=10; aIRR=4.72 (95%CI: 1.71-13.0) (Normal BMI:18.5-24.9) • Admission/after discharge: VTE=34; aIRR=1.00 (Overweight:25-29.9) • Time outside hospital: VTE=3; aIRR=9.42 (95%CI: 4.38-20.5) (Overweight:25-29.9) • Admission/after discharge: VTE=30; aIRR=1.00 (Obese:≥30) • Time outside hospital: VTE=5; aIRR=4.50 (95%CI: 1.23-16.4) (Obese:≥30)	
Full citation Virkus, R. A., Lokkegaard, E., Lidegaard, O., Langhoff-Roos, J., Nielsen, A. K., Rothman, K. J., Bergholt, T., Risk factors for venous thromboembolism in 1.3 million pregnancies: a nationwide prospective cohort, PLoS ONE [Electronic Resource], 9, e96495, 2014	**Cases** 748 VTE events **Diagnostic criteria** ICD-8 codes up to 1993, or ICD-10 codes thereafter **Controls** 1,296,289 pregnancies without VTE	**Factors** Definition of VTE: first occurrence of VTE during pregnancy or the puerperal period. • Included DVT of the lower or upper extremities, pulmonary embolism, cerebral venous thrombosis, portal vein thrombosis, vena cava thrombosis and ovarian vein thrombosis.	**Limitations** **QUIPS checklist** Study participation: Moderate risk (no baseline sample data reported, may likely introduce substantial bias) Study attrition: Low risk (attrition not issue given study based on registry data) Prognostic factor measurement: Moderate risk (missing data on smoking and BMI, smoking recorded only at beginning of pregnancy, unsure whether method and

Study details	Participants	Factors and results	Comments
Ref Id 386425 **Country/ies where the study was carried out** Denmark **Study type** Population based Retrospective cohort study **Study dates** 01/1995 to 12/2009 **Consecutive recruitment** Yes **Funding** Study funded by the research foundation at Hillerød Hospital, University of Copenhagen.	**Inclusion criteria** • All Danish women 15-49 years old during 1st January 1995 through 31 December 2009. • Pregnant women in this population identified in the National Registry of Patients. • First occurrence of VTE during pregnancy or the puerperal period, as noted in National Registry of Patients and the Causes of Deaths Registry. **Exclusion criteria** • History of VTE,other cardiovascular disease or cancer. **Statistical method** • Stratified analyses conducted to examine relations between each exposure and the main confounders. • Incidence rate of VTE calculated during pregnancy and puerperal period • Crude, age-adjusted and confounder-adjusted rate ratios with 95% CIs estimated using Poisson regression, and presented separately for	• Diagnosis considered validated if there was at least one relevant confirmatory diagnostic test result from ultrasonography, venography, ventilation-perfusion lung scan, computed tomography or magnetic resonance scan, or if the women received anticoagulation therapy in therapeutic doses for the rest of the pregnancy or puerperal period, or for at least 3 months. Exposures variables defined as hyperemesis; polyhydramnios; preeclampsia; infection based on antibiotic treatment; infection based on discharge diagnosis; plurality, BMI and smoking status; hospitalisation; preeclampsia or a hypertensive disorder; infection; intrauterine growth restriction/foetal death; bleeding episode during pregnancy (placenta previa or abruptio placentae); threatening preterm labour or preterm premature rupture of the membranes. Potential confounders defined as age; calendar year; parity; educational status; thrombophilia; anticoagulative prophylactic treatment; diabetes mellitus; inflammatory bowel disease; other inflammatory or rheumatoid disease; assisted reproductive technology. **Adjusted relative risk/odds ratio** Total number of VTE events=748 (433 VTE events in pregnancy; 315 events in puerperal period) **Multivariate analysis of adjusted incidence rate ratio (aIRR) between VTE and prognostic factors reported with 95%CI:** (adjusted for age, calendar-year, educational status, thrombophilia, anticoagulation treatment, medical diseases, assisted reproductive treatment and parity).	setting of factor measurement same for all participants, may likely introduce substantial bias) Outcome measurement: Low risk (VTE confirmed objectively, unsure whether method and setting of outcome measurement is the same for all participants, but unlikely to introduce substantial bias) Study confounding: High risk (Smoking and BMI not adjusted for due to inadequate data, unsure whether method and setting of measurement for confounders is the same for all participants, very likely to introduce substantial bias) Statistical analysis and reporting: Low risk (no areas of concern for this domain) **Overall quality: Low** **Other information** NOTE: The puerperal period comprised the 12 weeks after the delivery or 8 weeks after a pregnancy that was terminated early. NOTE: Woman's follow up was censored at death, emigration, diagnosis of cancer, diagnosis of any cardiovascular disease (including VTE). NOTE: Data not available for pregnancies that end before week 22.

Study details	Participants	Factors and results	Comments
	'during pregnancy' and 'puerperal period'. NOTE: Information on smoking, BMI, plurality and mode of delivery not available for pregnancies ending prior to week 22. • Dealt with the missing data on BMI prior to 2004 by restricting analysis on this variable to years when information was available. **Demographics** Data was collected on age, calendar year, parity, educational status, thrombophilia, anticoagulative prophylactic treatment, diabetes mellitus, inflammatory bowel disease, other infmlammatory or rheumatoid disease and assisted reproductive technology. No baseline demographics presented, and could not be calculated from information contained in paper.	**Smoking** • with VTE: n=318; Non-smoker= 1 as reference • Smoker n=73 aIRR=0.9 (95%CI 0.7-1.2); • Unknown aIRR=1.8 (95%CI 1.2-2.7). **BMI (kg/m2)** • <18.5: aIRR=0.9 (95% 0.4-2.0) • 18.5-24.9: aIRR=1 as reference • 25-29.9: aIRR=1.4 (95%CI 1.0-2.0) • 30-34.9: aIRR=1.0 (95%CI 0.6-1.8) • >35, aIRR=0.7 (95%CI 0.3-1.8) • Unknown, aIRR= 1.1 (95%CI 0.6-20). **Hyperemesis** • No hyperemesis: aIRR= 1 as reference; • During pregnancy aIRR=2.5 (95%CI 1.4-4.5). **Multiple pregnancy** • Singleton pregnancy: aIRR=1 as reference • Multiple pregnancy: aIRR=2.8 (95%CI 1.9-4.2). **Infection** • No antibiotic treatment: aIRR=1 as reference • Antibiotic treatment: aIRR=1.8 (95%1.5-2.3).	

Study details	Participants	Factors and results	Comments
		• No infection discharge diagnoses: aIRR= 1 as reference • Infection discharge diagnoses: aIRR=4.3 (95%CI 2.7-7.1). **Hospitalisation** • No hospitalisation: aIRR= 1 as reference • 1-2 days: aIRR=10.3 (95%CI 7.9-13.4) • 3-7 days: aIRR=12.2 (95%CI 8.7-17.0) • 8-14 days: aIRR=4.0 (95%CI 2.0-7.3) • >14 days: aIRR=3.3 (95%CI 2.6-4.2). **Pre-eclampsia** • No preeclampsia: aIRR= 1 reference • Preeclampsia: aIRR=1.2 (95%CI 0.4-3.6). Incidence rate – adjusted incidence rate per 10,000 women-years at risk. NB: Not adjusted for the analysis of women hospitalised for >1 day during pregnancy.	
Full citation Wang, C., Le Ray, I., Lee, B., Wikman, A., Reilly, M., Association of blood group and red blood cell transfusion with the incidence of antepartum, peripartum and postpartum venous thromboembolism, Scientific ReportsSci, 9, 13535, 2019	**Cases** 1,156 pregnancies with antepartum VTE **Diagnostic criteria** Based on ICD codes **Controls**	**Factors** Blood group with O as reference (A, B, AB as factors). Blood group with RhD+ as reference (Rh- as factor). Previous transfusion. Final model adjusted for calendar year, mother's country of origin, maternal age, smoking and multiple gestation. All information extracted from SCANDAT database.	**Limitations** **QUIPS checklist** Study participation: Low risk (no area of concerns for this domain) Study attrition: Low risk (attrition not an issue given study based on register) Prognostic factor measurement: Low risk (factors defined, objective and identified from register)

Study details	Participants	Factors and results	Comments
Ref Id 1250409 **Country/ies where the study was carried out** Sweden **Study type** Population based cohort **Study dates** 2001-2012 **Consecutive recruitment** Yes **Funding** Academic	999,841 pregnancies without antepartum VTE **Inclusion criteria** All valid delivery records from the MBR database in Sweden from 2001 to 2012, **Exclusion criteria** Excluded women with thrombophilia or inflammatory/rheumatic disease, unknown blood type, unknown country of origin, missing maternal smoking data, prior VTE **Statistical method** Included known risk factors (and additional not well established but plausible and some evidence of crude univariate association with a p value of <0.2) for VTE in multivariate logistic regression models. **Demographics** **Total number of women** 1,082,352 potentially eligible delivery records, of which 1,000,997 included **Maternal age at delivery** Mean 30.8, SD 5.2 **Parity** 43.4% nulliparous **Previous VTE** Excluded from this study **BMI** Mean 24.6, SD 4.4 **Blood group**	**Adjusted relative risk/odds ratio** Antepartum VTE: A (vs O): adjusted OR 1.78 (95% CI 1.55 to 2.04) B (vs O): adjusted OR 1.64 (95% CI 1.35 to 1.99) AB (vs O): adjusted OR 1.20 (95% CI 0.89 to 1.61) RhD-: adjusted OR 0.96 (95% CI 0.81 to 1.13) Prior RBC transfusion history: adjusted OR 1.41 (1.05 to 1.89)	Outcome measurement: High risk (unclear what methods would have been used to confirm VTE when recorded in register) Study confounding: Moderate risk (some key confounders captured and adjusted for in multivariate model but limited information on how the final model was selected) Statistical analysis and reporting: Low risk (no concerns) **Overall quality: Low**

Study details	Participants	Factors and results	Comments
	O = 38.2% A = 44.1% B = 12.4% AB = 5.2% Rh+ = 85.6% Prior transfusion = 3.0%		

BMI: body mass index, IBD: inflammatory bowel disease, IR: incidence rate, VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, (a)HR: (adjusted) hazard ratio, (a)IRR: (adjusted) incidence rate ratio, (a)OR: (adjusted) odds ratio, (a)RR: (adjusted) risk ratio/relative risk,

Appendix E – Forest plots

Forest plots for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

No evidence was identified which was appropriate for meta-analysis for this review question.

Appendix F – GRADE tables

GRADE tables for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Table 5: GRADE profile for independent association between acute respiratory tract infection and pregnancy-related VTE

Phase of investigation	A population based cohort study[1] which tested independent associations between a potential risk factor and the outcome of pregnancy-related VTE reported on this outcome. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was high risk of bias due to lack of objective diagnosis of VTE. There was also a moderate risk of bias due to an unreliable definition of BMI as a risk factor (using pre-pregnancy record).
Result	• [1]Sultan 2013: aIRR=1.65 (95%CI 0.94-2.90).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect. Evidence from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 6: GRADE profile for independent association between age (maternal) and pregnancy-related VTE

Phase of investigation	Five population based cohort studies[2,3,4,5,6] and 1 nested case control study[1] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE contributed to this outcome. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. Evidence were from studies with low qualities. There were high risks of bias in the 6 studies due to lack of adjustment for important confounders such as thromboprohylaxis[2,3,4,5], BMI[3,4], immobilisation[3], multiple pregnancies[3] and smoking[1,5]. There were also high risks of bias in 5 studies[2,3,4,5,6] due to lack of objective diagnosis of VTE. There were moderate risks of bias in 5 studies due to reasons such as: unreliable definition of risk factors (e.g use of pre-pregnancy BMI[2,6] and smoking record only at the beginning of pregnancy[5] or at first appointment of antenatal care[4]); inadequate definition of risk factors[3,5] (especially the BMI[5]); missing data on smoking[4], BMI[5] and ovarian hyperstimulation syndrome (OHSS)[5].
Result	• [1]Galanaud 2010: aOR=1.2 (95% CI: 1.1-1.3) F5 1691A non-carriers. • [2]Jensen 2013: <20: aHR=1.45 (95% CI: 0.80-2.62); 20-<30: aHR=1.00 as reference; 30-<35: aHR=1.01 (95% CI: 0.78-1.29); ≥35: aHR=1.31 (95% CI: 0.98-1.75). • [3]Kane 2013: Total estimate: aIRR=1.06 (95%CI: 1.01-1.11) : <25: Antenatal DVT= aIRR=1.0 as reference; 25-34: Antenatal DVT= aIRR=1.06 (95% CI: 0.93-1.20); ≥35: Antenatal DVT= aIRR=1.33 (95% CI: 1.10-1.60). • [4]Lindqvist 1999: ≤19: aOR=1.00 (95% CI: 0.5-1.9); 20-34: aOR=1.00 as reference; ≥35: aOR=1.00 (95% CI: 0.7-1.4). • [5]Rova 2012: <40: aOR=1 as reference; ≥40: aOR=2.10 (95% CI: 1.3-3.7). • [6]Sultan 2013: 15-24: aIRR=0.89 (95% CI 0.62-1.27); 25-34: aIRR=1 as reference; 35-44: aIRR=1.40 (95% CI 0.99-1.96).
Inconsistency	Serious heterogeneity. Whilst effect estimates for older age groups ≥35 years were in the same direction in 4 studies[2,3,5,6], one study[4] showed no difference. Meanwhile one study[1] indicated increased risk of VTE with age without specifying the age group; a report in the same direction with the total effect estimate was reported in another study[3]. The 95%CIs of the evidence in the age group (≥35) were overlapping. It was difficult to compare age groups ≤35 reported in studies due to the report of different age ranges. However, the effect estimates for the age groups ≤35 ranged between 1.0 to 1.45 with 95%CIs between 0.5 and 2.62. Effect estimate from only one study showed an effect estimate in an opposite direction for age group.
Indirectness	No indirectness. Majority of evidence was from women with pregnancies that did not have VTE associated with ectopic, miscarried and terminated pregnancies. However, reported of DVT in women with miscarried pregnancies was included in one study[1], whilst another study[5] reported VTE in women with IVF pregnancies as well as women with OHSS and not giving birth during the period of the study. Although there were only 2 studies that reported VTE from a broad range of characteristics of women, the evidence could be deemed to be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, OHSS: ovarian hyperstimulation syndrome, VTE: venous thromboembolism

Table 7: GRADE profile for independent association between antenatal haemorrhage and pregnancy-related VTE

Phase of investigation	A population based cohort study[1] which tested independent associations between a potential risk factor and the outcome of pregnancy-related VTE reported on this outcome. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. Evidence was from a study[1] with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE and no adjustment of confounders such as BMI, smoking, immobilisation, multiple pregnancies and thromboprophylaxis. There were also moderate risks of bias due to partial definition of risk factors.
Result	• [1]Kane 2013: aIRR=1.34; 95% CI: 1.09-1.64
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from 1[1] study.
Indirectness	Population is indirect. The evidence was from pregnancies leading to delivery but that did not include ectopic, miscarried and terminated pregnancies. Effect estimates on pulmonary embolism during pregnancy was unclear from article, hence only results of DVT in pregnancy was extracted for analysis. Therefore, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, DVT: deep vein thrombosis, MID: minimum important difference, VTE: venous thromboembolism

Table 8: GRADE profile for independent association between Blood groups and pregnancy-related VTE

Phase of investigation	Two nested case-control studies[1,2] and one population based cohort study[3], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from one study with acceptable quality[1] and two studies with low quality. There were high risks of bias due to lack of adjustment for important confounders such as thromboprophylaxis and smoking in two studies[2,3]. There were moderate risks of bias in two studies due to unreliable assessment of smoking at first antenatal visit[1], and missing of data for 20% of the participants[2]. There was a moderate risk of bias for uncertainty about the consensus approach used to determine the VTE diagnosis of some women with uncertain records, in 1 study[1] and high risk of bias for lack of objective diagnosis of VTE[2,3]. One of the studies also reported an atypical VTE (unspecified venous thrombosis) as part of the outcomes[2]. There was a moderate risk of bias in one study[2] due to inadequate report of baseline/demographic data.
	• [1]Larson 2005: A: aOR=3.9 (95% CI: 1.5-9.7); B: aOR=1.5 (95% CI: 0.4-5.5); AB: aOR=2.2 (95% CI: 0.4-12.5); O: aOR=1.0 as reference. • [2]Simpson 2001: A: aOR=1.9 (95% CI: 1.2-3.0); B: aOR=1.6 (95% CI: 0.9-2.9); AB: aOR=1.6 (95% CI: 0.6-4.1); O: aOR=1.0 as reference. • [3]Wang 2019: A: aOR=1.78 (95% CI: 1.55-2.04); B aOR=1.64 (95% CI: 1.35-1.99); AB: aOR=1.20 (95% CI:0.89-1.61); O: aOR=1.0 as reference. • [3]Wang 2019: RhD- vs RhD+: aOR=0.96 (95% CI: 0.81-1.13)
Inconsistency	No heterogeneity. The evidence was in the same direction with overlapping 95% CIs.
Indirectness	No indirectness, evidence from all studies was from pregnancies leading to birth. However, 1 study[2] also included report of VTE in pregnancies more than 24 weeks of gestation. Hence, the evidence may be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision for RhD-. Serious risk of imprecision, CI crossed 1 MID (1.25) for 2 of the 3 studies for blood group A only. Serious to very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25) for 2 of the 3 studies for blood groups B and AB.
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY FOR ABO OUTCOMES, LOW QUALITY FOR RHESUS

aOR: adjusted odds ratio, CI: confidence interval, MID: minimum important difference, RhD: Rhesus D, VTE: venous thromboembolism

Table 9: GRADE profile for independent association between BMI (kg/m^2) and pregnancy-related VTE

Phase of investigation	Two population based cohort studies[3,5] and 3 nested-case control studies[1,2,4] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE contributed to this outcome. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. Majority of the evidence were from studies with low qualities, except 1 study with acceptable quality[2]. There were high risks of bias in 4 studies due to lack of adjustment for important confounders such as thromboprohylaxis[,3,4], BMI[3,5], and smoking[1,3,4,5]. There were also high risks of bias in 2 studies due to the report of VTE without objective diagnosis[3,4], whilst another study[2] which reported objectively diagnosed VTE has a moderate risk of bias due to the consensus process of determining the VTE diagnosis of women with uncertain records. One of the studies also reported an atypical VTE (unspecified venous thrombosis) as part of the outcomes[4]. There were moderate risks of bias in 4 studies due to reasons such as: unreliable definition of risk factors (e.g. smoking record only at the beginning of pregnancy[3,5] or at first visit for antenatal care[2]); inadequate definition of risk factors[3] (BMI); missing data on smoking[5], BMI[3,4,5]; and ovarian hyperstimulation syndrome (OHSS)[5]. There were also moderate risks of bias in 2 studies due to inadequate[4] or lack[5] of demographic/baseline data report.
Result	• [1]Galanaud 2010: ≤25: aOR=1 as reference.>25: aOR=7.4 (95% CI: 3.1-17.7) F5 1691A non-carriers; >25: aOR=10.5 (95% CI: 1.5-73.5) F5 1691A carriers. • [2]Larsen 2007: <25: aOR=1.0 as reference; 25-30: aOR=1.6 (95% CI: 0.6-4.4); >30: aOR=9.7 (95% CI: 3.1-30.8). • [3]Rova 2012: <25: aOR=1.0 as reference; ≥25-<30: aOR=1.2 (95% CI: 0.8-1.8); ≥30: aOR=3.2 (95% CI: 2.2-4.6); Missing: aOR=1.3 (95% CI: 0.8-2.1). • [4]Simpson 2001: <20: aOR=0.4 (95% CI: 0.2-1.1); 20-24.99: aOR=1.0 as reference; 25-29.99: aOR=1.2 (95% CI: 0.8-2.0); ≥30: aOR=1.4 (95% CI: 0.7-2.6); Missing: aOR=1.0 (95% CI: 0.5-1.7). • [5]Virkus 2014: <18.5: aIRR=0.9 (95%CI 0.4-2.0); 18.5-24.9: aIRR=1 as reference; 25-29.9: aIRR=1.4 (95%CI 1.0-2.0); 30-34.9: aIRR=1.0 (95%CI 0.6-1.8); >35: aIRR=0.7 (95%CI 0.3-1.8); Unknown: aIRR=1.1 (95%CI 0.6-20).
Inconsistency	Very serious heterogeneity. Effect estimates for BMI ≥25 from studies were in the same direction with overlapping 95%CIs. The effect estimates ranged from 1.2 to 10.5 with 95% CIs from 0.6 to 73.5. However, evidence from 1 study[5] showed a decline in effect estimate for BMI ≥30 with no difference and in opposite direction for BMI ≥35 from 1.0 to 0.7

	respectively with overlapping 95%CIs from 0.3 to 1.8. Meanwhile 2 studies showed effect estimates in opposite direction for BMI<20[4] and BMI<18.5[5] ranging from 0.4 to 0.9 with overlapping 95%CI from 0.2 to 2.0.
Indirectness	No indirectness. Evidence from 1 studies[2] was from women with pregnancies that did not include VTE associated with ectopic, miscarried and terminated pregnancies. However, 1 study[1] included report for DVT in women with miscarried pregnancies, whilst another study[5] included report for VTE in women with early terminated pregnancies, and another study[3] reported VTE in women with IVF pregnancies as well as women with OHSS and those not giving birth during the period of the study. Another study[4] also included report of VTE in pregnancies more than 24 weeks of gestation. Hence, this evidence may adequately represent the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, DVT: deep vein thrombosis, MID: minimum important difference, OHSS: ovarian hyperstimulation syndrome, RhD: Rhesus D, VTE: venous thromboembolism

Table 10: GRADE profile for independent association between cancer (unspecified) and pregnancy-related VTE

Phase of investigation	One cohort study[1] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was high risk of bias due to lack of objective diagnosis of VTE. There was also a moderate risk of bias due to an unreliable definition of BMI as a risk factor with pre-pregnancy record.
Result	• [1]Sultan 2013: aIRR=1.95 (95%CI 0.86-4.41)
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from 1[1] study.
Indirectness	Population is indirect. Evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.

Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 11: GRADE profile for independent association between deprivation and pregnancy-related VTE

Phase of investigation	One cohort study[1] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE and no adjustment of confounders such as BMI, smoking, immobilisation, multiple pregnancies and thromboprohylaxis. There was also a moderate risk of bias due to partial definition of risk factors.
Result	• [1]Kane 2013: 1st quintile: DVT= aIRR=1.0 as reference (most affluent). • 2nd quintile: aIRR=0.98 (95% CI: 0.81-1.17). • 3rd quintile: aIRR=0.89 (95% CI: 0.74-1.07) • 4th quintile: aIRR=1.02; 95% CI: 0.85-1.22. • 5th quintile: aIRR=1.26; 95% CI: 1.06-1.49.
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population and outcome are indirect. The evidence was from pregnancies leading to delivery but that did not include VTE events associated with ectopic, miscarried and terminated pregnancies. Effect estimates on PE events during pregnancy was unclear from the article, hence only results of DVT in pregnancy was extracted for analysis. Therefore, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25) for 5th quintile. Serious risk of imprecision, CI crossed 1 MIDs (0.8) for 2nd quintile. No imprecision for 3rd and 4th quintiles.

Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, DVT: deep vein thrombosis, MID: minimum important difference, PE: pulmonary embolism, VTE: venous thromboembolism

Table 12: GRADE profile for independent association between gestational diabetes and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE, and due to lack of adjustment for thromboprohylaxis as a confounder. There was also a moderate risk of bias due to an unreliable definition of BMI with pre-pregnancy weight as a risk factor.
Result	• [1]Jensen 2013: aHR=1.52 (95% CI: 0.84-2.74).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect. Evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 13: GRADE profile for independent association between gestational hypertension and pregnancy-related VTE

Phase of investigation	Three cohort studies[1,2,3], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There was a high risk of bias in 1 of the studies[1] due to lack of adjustment for thromboprohylaxis. There was high risk of bias in outcome measurement for 1 study[3] as VTE was captured by those attending an anticoagulation clinic which may miss women who die or do not require treatment. There were also high risk of bias in 2 of the studies[1,2] due to lack of objective diagnosis of VTE. Two of the studies also have moderate risks of bias due to unreliable definition of risk factors such as BMI with pre-pregnancy weight[1,2]. One study[3] had a high risk of bias due to study confounding as only 3 confounders we considered, important possible confounding factors including smoking and BMI were not adjusted for.
Result	• [1]Jensen 2013: aHR=1.12 (95% CI: 0.52-2.40). • [2]Sultan 2013: aIRR=0.99 (95%CI 0.36-2.72). • [3]Scheres 2020: aHR=2.0 (95% CI: 1.7-2.4)
Inconsistency	Very serious heterogeneity, evidence was not in the same direction with some overlapping 95%CIs.
Indirectness	Population is indirect. The evidence from all studies was from pregnancies that did not include VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence may not be from an adequate representation of the general population of pregnant women. One study[3] included women with hypertension measured during pregnancy but did not distinguish between pre-existing and gestational hypertension, given the prevalence of pre-existing hypertension in this age group it was included in this outcome overall.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio; aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 14: GRADE profile for independent association between history of blood transfusion and pregnancy-related VTE

Phase of investigation	One cohort study[1] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to outcome measurement as it was unclear how VTE would have been confirmed when it was recorded in the register used for the study. There was a moderate risk of bias due to study confounding as it was not clear how the final model and confounders were chosen.
Result	• [1]Wang 2019: aOR=1.41 (95% CI: 1.05-1.89).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect, evidence from the study was from pregnancies that led to deliveries but did not include VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence may not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aOR: adjusted odds ratio, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 15: GRADE profile for independent association between history of VTE and pregnancy-related VTE

Phase of investigation	Two cohort studies[1,2] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in both studies due to lack of adjustment for important confounders such

	as thromboprophylaxis[1,2], BMI[2], immobilisation[2], smoking[2] and multiple pregnancies[2]. There were high risks of bias in both studies due to lack of objective diagnosis of VTE. There were moderate risks of bias in both studies due to unreliable definition of BMI with pre-pregnancy records[1,2], and partial definition of risk factors[2].
Result	• [1]Jensen 2013: aHR=72.65 (95% CI: 51.17-103.15). • [2]Kane 2013: aIRR=7.97 (95% CI: 6.30-10.10).
Inconsistency	Serious heterogeneity, evidence is in the same direction but with no overlapping 95%CIs.
Indirectness	Population is indirect, evidence from both studies was from pregnancies that led to deliveries but did not include VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence may not be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, VTE: venous thromboembolism

Table 16: GRADE profile for independent association between hospitalisation and pregnancy-related VTE

Phase of investigation	Two cohort studies[1,2], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias due to lack of adjustments for confounders such as smoking[1,2], and BMI[2]. There were moderate risks of bias in both studies due to unreliable definition of risk factors such as the use of pregnancy record for BMI[1], and smoking status assessed only at the beginning of pregnancy[2]. There was a high risk of bias in 1 study[1] due to lack of objective diagnosis of VTE and there was a moderate risk of bias in 1 study[2] due to lack of baseline/demographic data report.
Result	• [1]Sultan 2013a: Outside hospital: aIRR=1 as reference; Hospital admission: aIRR=17.5 (95% CI: 7.67-40.0); After discharge: aIRR=6.27 (95% CI: 3.74-10.5); <3days: aIRR=4.05 (95% CI: 2.23-7.38); ≥3days: 95%CIs: aIRR=12.2 (95% CI: 6.65-22.7).

	• [2]Virkus 2014: No hospitalisation: aIRR=1 as reference; 1-2 days aIRR=10.3 (95%CI 7.9-13.4); 3-7 days: aIRR=12.2 (95%CI 8.7-17.0); 8-14 days: aIRR=4.0 (95%CI 2.0-7.3); >14 days: aIRR= 3.3 (95%CI 2.6-4.2).
Inconsistency	No heterogeneity, evidence was in the same direction with some overlapping 95% CI.
Indirectness	No indirectness. Evidence from both studies was from pregnancies that led to delivery and 1 of the studies[1] included report of VTE in early terminated pregnancies. Hence, the evidence may be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, VTE: venous thromboembolism

Table 17: GRADE profile for independent association between hyperemesis and pregnancy-related VTE

Phase of investigation	Two cohort studies[1,2], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist. The evidence were from studies with low qualities. There were high risks of bias in both studies due to lack of adjustment for important confounders such as thromboprohylaxis[1], smoking[2] and BMI[2]. There were moderate risks of bias in both studies due to unreliable definition of BMI with pre-pregnancy record[1], smoking status recorded at the beginning of pregnancy[2], missing data on smoking[2] and BMI[2]. There was a high risk of bias in 1 study[1] due to lack of an objective diagnosis of VTE.
Result	• [1]Jensen 2013: aHR=2.40 (95% CI: 1.43-4.04). • [2]Virkus 2014: aIRR=2.5 (95% CI 1.4-4.5).
Inconsistency	No heterogeneity, evidence was in the same direction with overlapping 95%CIs.
Indirectness	No indirectness. Evidence from both studies was from pregnancies leading to delivery. However, 1 study[2] also reported VTE in early terminated pregnancies. Hence, the evidence might be from an adequate representation of the general population of pregnant women.

Imprecision	No imprecision
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: LOW QUALITY

aIRR: adjusted incidence rate ratio, aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, VTE: venous thromboembolism

Table 18: GRADE profile for independent association between infection (unspecified) and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of confounding for BMI and smoking as confounders. There was also a moderate risk of bias due to unreliable assessment of smoking only at the beginning of pregnancy and due to missing data of BMI and smoking as risk factors. There was a moderate risk of bias due to no report of baseline/demographic data.
Result	• [1]Virkus 2014 • Antibiotic treatment aIRR=1.8 (95%CI 1.5-2.3). • Infection discharge diagnoses aIRR=4.3 (95%CI 2.7-7.1).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from 1[1] study.
Indirectness	No indirectness. Evidence was from pregnancies leading to birth and early terminated pregnancies. Hence, the evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.

Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, VTE: venous thromboembolism

Table 19: GRADE profile for independent association between inflammatory bowel disease and pregnancy-related VTE

Phase of investigation	Two cohort studies[1,2], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in both studies due to lack of adjustment for important confounders such as thromboprohylaxis[2] and drugs used to treat IBD[1]. There were high risks of bias in both studies due to lack of objective diagnosis of VTE. Both studies also have moderate risks of bias due to unreliable definition of BMI with pre-pregnancy record[1,2] and missing data for BMI[1] and smoking[1].
Result	• [1]Hansen 2017: aRR 1.61 (95% CI 1.01-2.56). • [2]Sultan 2013: aIRR 3.50 (95% CI 1.12-10.9).
Inconsistency	No heterogeneity, evidence was in the same direction with overlapping 95%CIs.
Indirectness	Population is indirect, evidence from both studies was from pregnancies leading to delivery but did not include reports for VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence may not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of bias, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, aRR: adjusted risk ratio, BMI: body mass index, CI: confidence interval, IBD: inflammatory bowel disease, MID: minimum important difference, VTE: venous thromboembolism

Table 20: GRADE profile for independent association between in-vitro fertilisation and pregnancy-related VTE

Phase of investigation	One cohort study[1], which test independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was high risk of bias due to lack of objective diagnosis of VTE and a high risk of bias due to lack of adjustment for thromboprohylaxis and smoking as confounders. There was also a moderate risk of bias due to lack of definition of BMI as a risk factor and an unreliable assessment of smoking only at the beginning of pregnancy, as well as a high number of missing BMI and ovarian hyperstimulation syndrome (OHSS) data.
Result	• [1]Rova 2012 • Not IVF: aOR=1 as reference. • Frozen embryo replacement cycle (FER) aOR=1.6 (95%CI 0.2-11.3). • Fresh IVF not OHSS: aOR=4.7 (95%CI 2.6-8.4). • Fresh IVF and OHSS: aOR=101.0 (95%CI 62.5-163.3).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	No indirectness, evidence was from a general population of women including women with IVF who gave birth and those with OHSS but who did not give birth. Hence, the evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious imprecision, CI crossed 2 MIDs (0.8 and 1.25) for FER. No imprecision for Fresh IVF with and without OHSS.
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, FER: frozen embryo replacement, IVF: in vitro fertilisation, MID: minimum important difference, OHSS: ovarian hyperstimulation syndrome, VTE: venous thromboembolism

Table 21: GRADE profile for independent association between medications and pregnancy-related VTE

Phase of investigation	One cohort study[1], which test independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE, and due to lack of adjustment for thromboprohylaxis as a confounder. There was also a moderate risk of bias due to an unreliable definition of BMI with pre-pregnancy weight as a risk factor.
Result	[1]Jensen 2013: • A01AC: Corticosteroids for local treatment: aHR=6.48 (95% CI 0.91-46.28), p-value=0.222 • A02AD: Combinations and complexes of aluminium, calcium and magnesium compounds: aHR=1.13 (95% CI 0.16-8.09), p-value= 0.939 • A02BA: H2-receptor antagonists: aHR=2.21 (95% CI 0.82-5.95), p-value=0.310 • A02BC: Proton pump inhibitors: aHR=2.58 (95% CI 1.47-4.53), p-value=0.012 • A02BX: Other drugs peptic ulcer and gastro-oesophageal reflux disease: aHR=2.24 (95% CI 0.31-15.95), p-value=0.581 • A03AA: Synt anticholinergic, esters with tertiary amino group: aHR=12.96 (95% CI 1.82-92.33), p-value=0.060 • A03FA: Propulsives: aHR=1.36 (95% CI 0.85-2.20), p-value=0.426 • A04AA: Serotonin (5HT3) antgonists: aHR=1.67 (95% CI 0.56-4.99), p-value=0.537 • A06AB: Contact laxatives: aHR=2.11 (95% CI 0.28-16.02), p-value=0.612 • A06AG: Enemas: aHR=2.92 (95% CI 0.41-21.08), p-value=0.509 • A07AA: Antibiotics: aHR=3.09 (95% CI 0.43-22.01), p-value=0.480 • A07EC: Aminosalicylic acid and similar agents: aHR=7.07 (95% CI 2.63-18.99), p-value=0.004 • A08AA: Centrally acting antiobesity products: aHR=4.36 (95% CI 0.60-31.54), p-value=0.371 • A10AB: Insulins and analogues for injections, fast acting: aHR=2.57 (95% CI 0.36-18.51), p-value=0.537 • A10AD: Insulins and analogues for injection intermediate-acting combined with fast-acting: aHR=8.09 (95% CI 1.86-35.13), p-value=0.040 • A10AE: Insulins and analogues for injection, long-acting: aHR=7.79 (95% CI 1.08-56.46), p-value=0.161 • A10BA: Biguanides: aHR=0.58 (95% CI 0.08-4.17), p-value=0.726 • A11E: Vitamin b-complex, including combinations: aHR=5.54 (95% CI 0.77-39.79), p-value=0.277 • B03AA: Iron bivalent, oral preparations: aHR=0.85 (95% CI 0.12-6.03), p-value=0.939 • B03BA: Vitamin B12 (cyanocobalamin and derivatives): aHR=1.35 (95% CI 0.43-4.26), p-value=0.731 • B03BB: Folic acid and derivatives: aHR=1.54 (95% CI 0.38-6.18), p-value=0.678 • C02AB: Methyldopa: aHR=2.24 (95%CI 0.31-16.45), p-value=0.581 • C03AB: Thiazides and potassium in combination: aHR=2.21 (95% CI 0.31-15.79), p-value=0.581 • C03EA: Low-ceiling diuretics and potassium-sparing agents: aHR=39.15 (95% CI 5.44-281.98), p-value=0.006 • C05AA: Corticosteroids: aHR=1.37 (95% CI 0.84-2.24), p-value=0.429

	• C05BA: Heparins or heparinoids for topical use: aHR=15.75 (95% CI 7.74-32.05), p-value=<0.001 • C07AB: Beta blocking agents: aHR=4.22 (95% CI 0.59-30.16), p-value= 0.371 • C07AG: Alpha- and beta blocking agents: aHR=1.25 (95% CI 0.17-8.98), p-value=0.932 • D01AC: Imidazole and triazole derivatives: aHR=1.88 (95% CI 1.15-3.06), p-value=0.062 • D01AE: Other antifungals for topical use: aHR=0.82 (95% CI 0.12-5.85), p-value=0.935 • D02AC: Soft paraffin and fat products: aHR=33.38 (95% CI 4.67-238.46), p-value=0.008 • D04AB: Anesthetics for topical use: aHR=15.82 (95% CI 2.22-112.87), p-value=0.040 • D06AX: Other antibiotics for topical use: aHR=2.13 (95% CI 1.01-4.51), p-value=0.176 • D06BB: Antivirals: aHR=1.20 (95% CI 0.30-4.81), p-value=0.917 • D07AA: Corticosteroids, weak (group i): aHR=2.90 (95% CI 1.08-7.78), p-value=0.143 • D07AB: Corticosteroids, moderately potent (group ii): aHR=0.75 (95% CI 0.31-1.82), p-value=0.661 • D07AC: Corticosteroids, potent (group iii): aHR=1.47 (95% CI 0.70-3.12), p-value=0.530 • D07BB: Corticosteroids, moderately potent, combination with antiseptic: aHR=3.17 (95% CI 0.79-12.75), p-value=0.299 • D07BC: Corticosteroids, potent, combination with antiseptic: aHR=2.74 (95% CI 0.38-19.56), p-value=0.530 • D07CB: Corticosteroids, moderately potent, combination with antibiotic: aHR=6.40 (95% CI 1.59-25.74), p-value=0.054 • D07CC: Corticosteroids, potent, combination with antibiotic: aHR=2.20 (95% CI 0.70-6.86), p-value=0.430 • D10AF: Anti-infectives for treatment of acne: aHR=2.23 (95% CI 0.72-6.98), p-value=0.399 • G01AF: Imidazole derivatives: aHR:1.73 (1.18-2.54), p-value=0.040 • G03AA: Progestogens and estrogens, fixed combinations: aHR=0.91 (95% CI 0.23-3.66), p-value=0.939 • G03AC: Progestogens: aHR=2.06 (95% CI 0.28-14.99), p-value=0.614 • G03CA:Natural and semisynthetic oestrogens, plain: aHR: 3.34 (95% CI 1.48-7.55), p-value=0.035 • G03DA: Pregnen: aHR= 3.22 (95% CI 1.97-5.52), p-value=0.001 • G03GA: Gonadotrophins: aHR=1.39 (95% CI 0.69-2.82), p-value=0.537 • G03GB: Ovulation stimulants, synthetic: 0.88 (95% CI 0.12-6.29), p-value=0.939 • H01CC: Anti gonadotrophin releasing hormones: aHR=2.80 (95% CI 0.69-11.31), p-value=0.371 • H02AB: Glucocorticoids: aHR=2.14 (95% CI 0.68-6.68), p-value=0.419 • H03AA: Thyroid hormones: aHR=1.52 (95% CI 0.41-5.61), p-value=0.661 • H03BB: Sulphur-containing imidazole derivatives: aHR=3.15 (95% CI 0.44-22.49), p-value=0.472 • H04AA: Glycogenolytic hormones: aHR=2.54 (95% CI 0.35-18.16), p-value=0.537 • J01CA: Penicillins with extended spectrum: aHR=1.71 (95% CI 1.29-2.27), p-value=0.005 • J01CE: Beta-lactamase sensitive pencillins: aHR=1.47 (95% CI 1.06-2.04), p-value= 0.103 • J01CF: Beta-lactamase resistant penicillins: aHR=2.31 (95% CI 0.86-6.21), p-value=0.292 • J01EB: Short-acting sulphonamides: aHR=1.36 (95% CI 0.87-2.13), p-value=0.403 • J01FA: Macrolides: aHR= 2.24 (95% CI 1.28-3.92), p-value=0.039 • J01XE: Nitrofuran derivatives: aHR=1.61 (95% CI 0.66-3.90), p-value=0.516 • J02AC: Triazole derivatives: aHR=1.13 (95% CI 0.36-3.53), p-value=0.932

	• J05AB: Nucleosides and nucleotides excluding reverse transcriptase inhibitors: aHR=2.29 (95% CI 0.85-6.14), p-value=0.296 • J05AH: Neuraminidase inhibitors: aHR=1.51 (0.21-10.77), p-value=0.800 • J06BA: Immunoglobulins, normal human: aHR=5.95 (0.84-42.43), p-value=0.249 • J07BM: Papillomavirus vaccines: aHR=18.42 (95% CI 2.57-132.05), p-value= 0.035 • L04AX: Other immunosuppressants: aHR=4.85 (95% CI 0.68-34.72), p-value=0.310 • M01AB: Acetic acid derivatives and related substances: aHR=1.62 (95% CI 0.52-5.04), p-value=0.576 • M01AE: Propionic acid derivatives: aHR=1.24 (95% CI 0.55-2.79), p-value=0.730 • M01AX: Other anti-inflammatory/ anti-rheumatic agents, mom-steroids: aHR=12.78 (95% CI 1.79-91.12), p-value=0.060 • M02AA: Anti-inflammatory preparations, non-steroids for topical use: aHR=3.73 (95% CI 0.53-26.65), p-value=0.419 • N02AA: Natural opium alkaloids: aHR=1.73 (95% CI 0.42-6.95), p-value=0.588 • N02AX: Other opioids: aHR=1.71 (95% CI 0.42-6.89), p-value=0.595 • N02BE: Anilides: aHR=1.84 (95% CI 0.59-5.75), p-value=0.516 • N02CC: Selective 5HT(1)-receptor agonists: aHR=0.89 (95% CI 0.13-6.37), p-value=0.939 • N03AE: Benzodiazepine derivatives: aHR=8.62 (95% CI 1.20-61.61, p-value=0.137 • N05AF: Carboxamide derivatives: aHR=8.76 (95% CI 1.23-62.49), p-value=0.137 • N05BA: Benzodiazepine derivatives: aHR=4.52 (95% CI 1.86-11.00), p-value=0.012 • N05CF: Benzodiazepine related drugs: aHR=2.52 (95% CI 1.13-11.01), p-value=0.137 • N06AB: Selective serotonin reuptake inhibitors: aHR=1.52 (95% CI 0.78-2.97), p-value=0.429 • N06BA: Centrally acting sympathomimetics: aHR=6.34 (95% CI 0.88-45.47), p-value=0.228 • N07BC: Drugs used in opioid dependence: aHR=8.25 (95% CI 1.13-6.39), p-value=0.939 • P01AB: Nitroimidazole derivatives: aHR=1.63 (95% CI 0.52-5.07), p-value=0.575 • P02CA: Benzimidazole derivatives: aHR=0.89 (95% CI 0.13-6.39), p-value=0.939 • P02CX: Other antiematodals: aHR=3.14 (95% CI 0.78-12.67), p-value=0.302 • R01AC: Antiallergic agents, excluding corticosteroids: aHR=1.20 (95% CI 0.17-8.58), p-value=0.935 • R01AD: Corticosteroids: aHR=1.34 (95% CI 0.75-2.38), p-value=0.537 • R03AC: Selective beta-2-adrenoceptor agonists: aHR=2.23 (95% CI 1.33-3.76), p-value=0.029 • R03AK: Adrenergics and other drugs for obstructive airway diseases: aHR=1.66 (95% CI 0.53-5.18), p-value=0.565 • R03BA: Glucocorticoids: aHR=1.67 (95% CI 0.74-3.74), p-value=0.439 • R03CC: Selective beta-2-adrenoreceptor agonists: aHR=3.59 (95% CI 0.50-25.59), p-values= 0.426 • R05DA: Opium alkaloids and derivatives: aHR=2.79 (95% CI 1.31-5.93), p-value=0.049 • R05FA: Opium derivatives and expectorants: aHR=2.00 (95% CI 0.50-8.05), p-value=0.537 • R06AD: Phenothiazine derivatives: aHR=2.36 (95% CI 0.33-16.85), p-value=0.570 • R06AE: Piperazine derivatives: aHR=1.19 (95% CI 0.53-2.68), p-value=0.799 • R06AX: Other antihistamines for systemic use: aHR=1.15 (95% CI 0.43-3.09), p-value=0.903

	• S01AA: Antibiotics: aHR=0.55 (95% CI 0.21-1.48), p-value=0.449 • S01AX: Other anti-infectives: aHR=5.86 (95% CI 0.82-41.8), p-value=0.250 • S01BA: Corticosteroids, plain: aHR=2.51 (95% CI 0.35-17.9), p-value=0.537 • S01GA: Sympathomimetics used as decongestants: aHR=1.04 (95% CI 0.26-4.18), p-value=0.975 • S01GX: Other anti-allergics: aHR=0.98 (95% CI 0.32-3.07), p-value=0.988 • S02CA: Corticosteroids and anti-infectives in combination: aHR=1.01 (95% CI 0.14-7.22), p-value=0.989 • S03CA: Corticosteroids and anti-infectives in combination: aHR=1.92 (95% CI 0.48-7.70), p-value=0.537
	No heterogeneity, given evidence for the 16 reported redeemed medications was from one study.
Indirectness	Population and outcome are indirect. The evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women. It is also not certain if the redeemed medications were actually taken by the pregnant women.
Imprecision	Very serious imprecision, CI crossed 2 MIDs (0.8 and 1.25) for the majority of medications listed
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 22: GRADE profile for independent association between miscarriage and pregnancy-related VTE

Phase of investigation	One nested case control study[1], which test independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with a low quality. There was a high risk of bias due to lack of adjustment for smoking as a confounder.
Result	• [1]Galanaud 2010: aOR=96.8 (95% CI: 10.2-916.7) F5 1691A non-carriers
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.

Indirectness	No indirectness, evidence was from pregnancies leading to birth and miscarried pregnancies. Hence, evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: LOW QUALITY

aOR: adjusted odds ratio, CI: confidence interval, VTE: venous thromboembolism

Table 23: GRADE profile for independent association between multiple pregnancy and pregnancy-related VTE

Phase of investigation	Three cohort studies[1,3,4] and 1 nested case-control study[2] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the evidence as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in the 4 studies due to lack of adjustment for important confounders such as thromboprohylaxis[1,2,], BMI[2,4], and smoking[4]. There were also high risks of bias due to lack of objective diagnosis of VTE in 3 studies[1,2,3], and 1 of the studies reported an atypical VTE (unspecified venous thrombosis) as part of the outcomes[2]. There were moderate risks of bias in the 4 studies due to unreliable definition of risk factors (especially use of pre-pregnancy BMI[3], smoking status recorded only at the beginning of pregnancy [4]), and missing BMI[2,4] and smoking data[2]. There was a moderate risks of bias in 2 studies[4] due to lack of report of demographic/baseline data or inadequate baseline data report[2].
Result	• [1]Lindqvist 1999: aOR=2.10 (95% CI: 1.0-4.6). • [2]Simpson 2001: ≥2: aOR= 4.2 (95% CI: 1.8-9.7). • [3]Sultan 2013: aIRR=0.83 (95%CI 0.26-2.60). • [4]Virkus 2014: Multiple pregnancy aIRR=2.8 (95%CI 1.9-4.2).
Inconsistency	Very serious heterogeneity. Evidence was mostly in the same direction, except from 1 study[3], which was in opposite direction. However, the 95%CIs were overlapping.

Indirectness	No indirectness. Evidence from 2 studies[1,3] was from pregnancies that did not include VTE events associated with ectopic, miscarried and terminated pregnancies. However, 1 study[4] reported VTE events in early terminated pregnancies and another study[2] included report of VTE in pregnancies more than 24 weeks of gestation. There is therefore a likelihood that the evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 24: GRADE profile for independent association between parity and pregnancy-related VTE

Phase of investigation	Four cohort studies[1,2,3,4] which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in the 4 studies due to lack of adjustment for important confounders such as thromboprohylaxis[1,2,3], BMI[2,3], immobilisation[2], multiple pregnancies[2] and smoking[2]. There were also high risks of bias in the 4 studies due to lack of objective diagnosis of VTE. There were moderate risks of bias in the 4 studies due to reasons such as: unreliable definition of risk factors (e.g use of pre-pregnancy BMI[1,4] and smoking record only at the first antenatal care visit[3]); inadequate definition of risk factors such as missing data on smoking[3]; partial definition of risk factors[2].
Result	• [1]Jensen 2013: 1st: aHR=1.00 as reference; 2nd: aHR-0.80(95% CI: 0.61-1.06); ≥3rd: aHR-0.98 (95% CI: 0.72-1.33). • [2]Kane 2013: 0: aIRR=1.00 as reference; 1-2: aIRR=0.80 (95 CI: 0.71-0.90); ≥3: aIRR=1.19 (95 CI: 0.96-1.46). • [3]Lindqvist 1999: Para 0: aOR=2.90 (95% CI: 2.1-3.9); Para 1: aOR=1.00 as reference; Para 2: aOR=1.30 (95% CI: 0.8-2.0); Para ≥3: aOR=2.80 (95% CI: 1.8-4.4). • [4]Sultan 2013: 1: aIRR=0.72 (95%CI 0.53-0.98); 2: aIRR=0.71 (95%CI 0.43-1.16); ≥3: aIRR=0.89 (95%CI 0.45-1.78).
Inconsistency	Very serious heterogeneity, evidence was not in the same direction, and without overlapping 95%CIs.

Indirectness	Population is indirect, evidence from the studies was from pregnancies that did not include VTE events associated with ectopic, miscarried and terminated pregnancies. Hence the evidence supporting the finding may not be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 25: GRADE profile for independent association between pre-eclampsia and pregnancy-related VTE

Phase of investigation	Five cohort studies[1,2,3,4,5], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in the 5 studies due to lack of adjustment for important confounders such as thromboprohylaxis[1,2,3,4], BMI[2,3,4,5], immobilisation[2,4], multiple pregnancies[2,4] and smoking[2,4,5]. There were also high risks of bias in 3 studies due to lack of objective diagnosis of VTE and 1 study because only VTEs that meant women attended anticoagulation clinics were assessed[4]. There were moderate risks of bias in the 4 studies due to reasons such as: unreliable definition of risk factors (e.g use of pre-pregnancy BMI[1] and smoking record only at the beginning of pregnancy[5] or at first antenatal care visit[3]); inadequate definition of risk factors such as missing data on BMI[5] and smoking[3,5]; partial definition of risk factors[2]. There was a moderate risks of bias in 1 studies[5] due to lack of report of demographic/baseline data.
Result	• [1]Jensen 2013: aHR=1.09 (95% CI: 0.58-2.04). • [2]Kane 2013: aIRR=1.03 (95% CI: 0.76-1.39). • [3]Lindqvist 1999: aOR=0.80 (95% CI: 0.4-1.6). • [4]Scheres 2020: aHR=7.8 (95% CI: 5.4-11.3). • [5]Virkus 2014: aIRR=1.2 (95%CI 0.4-3.6).

Inconsistency	Very serious heterogeneity, evidence was not in the same direction, but with overlapping 95%CIs.
Indirectness	No indirectness, evidence from most studies was from pregnancies that did not include VTE associated with ectopic, miscarried and terminated pregnancies. However, 1 of the studies[5] reported VTE in women who had early terminated pregnancies in addition to pregnancies leading to delivery. Hence, evidence contributing to the finding may be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 26: GRADE profile for independent association between pre-existing diabetes (unspecified) and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was high risk of bias due to lack of objective diagnosis of VTE. There was also a moderate risk of bias due to an unreliable definition of BMI as a risk factor (using pre-pregnancy record).
Result	• [1]Sultan 2013: aIRR=3.54 (95%CI 1.13-11.0).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect, evidence from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).

Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 27: GRADE profile for independent association between pre-existing hypertension and pregnancy-related VTE

Phase of investigation	Two cohort studies[1,2], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from studies with low qualities. There were high risks of bias in 1 study due to lack of adjustment for important confounders such as BMI[1], smoking[1], immobilisation[1], multiple pregnancies[1] and thromboprophylaxis[1]. There were also high risks of bias due to lack of objective diagnosis of VTE in both studies. There were also moderate risks of bias in the 2 studies due to unreliable measurement of risk factor (BMI[2]) or partial definition of the factors[1].
Result	• [1]Kane 2013: aIRR=1.18 (95%CI: 0.96-1.44). • [2]Sultan 2013: aIRR=0.74 (95%CI 0.32-1.71).
Inconsistency	Very serious heterogeneity, evidence was not in the same direction, but with overlapping 95%CIs.
Indirectness	Population is indirect, evidence from both studies was from pregnancies leading to deliveries but that did not include VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence may not be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 28: GRADE profile for independent association between smoking and pregnancy-related VTE

Phase of investigation	Four cohort studies[1,3,4,5] and 1 nested case-control study[2], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. Majority of the evidence was from studies with low qualities except 1 study with acceptable quality[2]. There were high risks of bias in 3 studies due to lack of adjustment for important confounders such as thromboprohylaxis[1,3], BMI[3,5], and smoking[5]. There were also high risks of bias due to lack of objective diagnosis of VTE in 3 studies[1,3,4], and moderate risk of bias in 1 study[2] due to the consensus process of determining the VTE diagnosis of women with uncertain records. There were moderate risks of bias in the 5 studies due to unreliable definition of risk factors (especially use of pre-pregnancy BMI[1,2,4], smoking status recorded only at the beginning of pregnancy[5] or first antenatal care visit[2,3]). There were a moderate risks of bias in 1 studies[5] due to lack of report of demographic/baseline data.
Result	• [1]Jensen 2013: Not-smoking: aHR=1.0 as reference; smoking: aHR=1.15 (95% CI: 0.87-1.52). • [2]Larsen 2007: Non-smokers: aOR=1.0 as reference; current smokers: aOR=5.7 (95% CI: 2.5-13.2). • [3]Lindqvist 1999: 0: aOR=1.00 as reference; 1-9: aOR=1.10 (95% CI: 0.8-1.5); ≥10: aOR=1.30 (95% CI: 0.9-2.0). • [4]Sultan 2013: aIRR=1.16 (95%CI 0.84-1.60). • [5]Virkus 2014: Non-smoker: aIRR=1 as reference; smoker 0.9 (95%CI 0.7-1.2); Unknown status: aIRR= 1.8 (95%CI 1.2-2.7).
Inconsistency	Very serious heterogeneity, evidence was mostly in the same direction except for 1 study[5] with effect estimate in an opposite direction. Some 95%CIs of the effect estimates were not overlapping. However, the effect estimate of VTE in women with unknown smoking status in the only study[5] which showed estimate in an opposite direction showed an independent association with increased risk of VTE in pregnancy. Hence, the heterogeneity could be due to the high population with missing data from the study[5].
Indirectness	No indirectness. Evidence from most studies was from pregnancies that do not include VTE associated with ectopic, miscarried and terminated pregnancies. However, only 1 study[5] reported VTE events in women with early terminated pregnancies as well as pregnancies leading to deliveries. Hence, the population producing the evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias. Given that the evidence was reported from a small number of studies.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, aIRR: adjusted incidence rate ratio, aOR: adjusted odds ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 29: GRADE profile for independent association between stroke and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE, and due to lack of adjustment for thromboprohylaxis as a confounder. There was also a moderate risk of bias due to an unreliable definition of BMI with pre-pregnancy weight as a risk factor.
Result	• [1]Jensen 2013: aHR=4.41 (95% CI: 0.71-27.29).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect, evidence was from pregnancies leading to delivery but did not include report of VTE in ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 30: GRADE profile for independent association between thrombophilia (unspecified) and pregnancy-related VTE

Phase of investigation	One cohort study[1], which test independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE, and due to lack of adjustment for thromboprohylaxis as a confounder. There was also a moderate risk of bias due to an unreliable definition of BMI with pre-pregnancy weight as a risk factor.
Result	• [1]Jensen 2013: aHR=1.30 (95% CI 0.47-3.66).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect, evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 26: GRADE profile for independent association between thrombophilia F2 20210 A (mother) and pregnancy-related VTE

Phase of investigation	One nested case-control study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with a low quality. There was a high risk of bias due to lack of adjustment for smoking as a confounder.

Result	• [1]Galanaud 2010: aOR=16.3 (95% CI: 6.3-42.3) F5 1691A non-carriers
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	No indirectness, evidence was from pregnancies leading to birth or miscarried pregnancies. Hence, evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: LOW QUALITY

aOR: adjusted odds ratio, CI: confidence interval, VTE: venous thromboembolism

Table 27: GRADE profile for independent association between thrombophilia F12 46T (mother) and pregnancy-related VTE

Phase of investigation	One nested case-control study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with a low quality. There was a high risk of bias due to lack of adjustment for smoking as a confounder.
Result	• [1]Galanaud 2010: aOR=2.8 (95% CI: 1.3-5.8) F5 1691A non-carriers.
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study**.**
Indirectness	No indirectness, evidence was from pregnancies leading to birth or miscarried pregnancies. Hence, evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: LOW QUALITY

aOR: adjusted odds ratio, CI: confidence interval, VTE: venous thromboembolism

Table 33: GRADE profile for independent association between thrombophilia PROCR 6936G (mother) and pregnancy-related VTE

Phase of investigation	One nested case-control study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with a low quality. There was a high risk of bias due to lack of adjustment for smoking as a confounder.
Result	• [1]Galanaud 2010: aOR= 2.5 (95% CI: 1.20-5.4) F5 1691A non-carriers. • aOR=0.7 (95% CI: 0.1-9.9) F5 1691A carriers.
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	No indirectness, evidence was from pregnancies leading to birth or miscarried pregnancies. Hence, evidence might be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision, CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aOR: adjusted odds ratio, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 34: GRADE profile for independent association between urinary tract infection and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE. There was also a moderate risk of bias due to an unreliable definition of BMI as a risk factor (using pre-pregnancy record).
Result	• [1]Sultan 2013: aIRR=1.80 (95%CI 1.22-2.67).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect. Evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Serious risk of imprecision, CI crossed 1 MID (1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 35: GRADE profile for independent association between vascular disease and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE, and due to lack of adjustment for thromboprohylaxis as a confounder. There was also a moderate risk of bias due to an unreliable definition of BMI with pre-pregnancy weight as a risk factor.
Result	• [1]Jensen 2013: aHR=2.71 (95% CI 0.20-37.63).

Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect. Evidence was from pregnancies leading to delivery but did not include report of VTE in ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	Very serious risk of imprecision. CI crossed 2 MIDs (0.8 and 1.25).
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.
Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aHR: adjusted hazard ratio, BMI: body mass index, CI: confidence interval, MID: minimum important difference, VTE: venous thromboembolism

Table 36: GRADE profile for independent association between varicose veins and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE. There was also a moderate risk of bias due to an unreliable definition of BMI as a risk factor (using pre-pregnancy record).
Result	• [1]Sultan 2013: aIRR=2.21 (95%CI 1.55-4.76).
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study.
Indirectness	Population is indirect. Evidence was from pregnancies leading to delivery but did not include report of VTE associated with ectopic, miscarried and terminated pregnancies. Hence, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, not applicable for factors without gradient of categories.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, VTE: venous thromboembolism

Table 37: GRADE profile for independent association between year of delivery and pregnancy-related VTE

Phase of investigation	One cohort study[1], which tested independent associations between potential risk factors and the outcome of pregnancy-related VTE. The evidence for this potential risk factor was therefore initially rated as high.
Study limitations	Serious risk of bias in the evidence contributing to the outcome as per QUIPS checklist. The evidence was from a study with low quality. There was a high risk of bias due to lack of objective diagnosis of VTE and no adjustment for confounders such as BMI, smoking, immobilisation, multiple pregnancies and thromboprohylaxis. There were also moderate risks of bias due to partial definition of risk factors.
	• [1]Kane 2013: Total estimate=aIRR=1.09 (95%CI: 1.05-1.14) • 1980-1985: aIRR=1-Reference • 1986-1990: aIRR=0.97 (95%CI: 0.82-1.15) • 1991-1995: aIRR=0.86 (95%CI: 0.72-1.03) • 1996-2000: aIRR=1.00 (95%CI: 0.84-1.20) • 2001-2005: aIRR=1.49 (95%CI: 1.26-1.76)
Inconsistency	No heterogeneity, unable to determine consistency since evidence emerged from one study: aIRR=1.09 (95%CI: 1.05-1.14).
Indirectness	Population and outcome are indirect. Evidence was from pregnancies leading to delivery but that did not include VTE associated with ectopic, miscarried and terminated pregnancies. Effect estimates on PE events during pregnancy was unclear from the article, hence only results of DVT in pregnancy was extracted for analysis. Therefore, the evidence might not be from an adequate representation of the general population of pregnant women.
Imprecision	No imprecision.
Publication bias	Serious risk of publication bias, given that evidence was reported from a single study.

Moderate or large effect size	Evidence not upgraded, given that outcome is downgraded in other domains.
Exposure-response gradient	Evidence not upgraded, given that outcome is downgraded in other domains.

OVERALL GRADE RATING: VERY LOW QUALITY

aIRR: adjusted incidence rate ratio, BMI: body mass index, CI: confidence interval, PE: pulmonary embolism, VTE: venous thromboembolism

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

No evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

Clinical studies

Table 38: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Aaron, S., Alexander, M., Maya, T., Mathew, V., Goel, M., Nair, S. C., Mammen, J., Vikram, M., Underlying prothrombotic states in pregnancy associated cerebral venous thrombosis, Neurology India, 58, 555-559, 2010	Cohort study no relevant data
Abbasi,N., Balayla,J., Laporta,D.P., Kezouh,A., Abenhaim,H.A., Trends, risk factors and mortality among women with venous thromboembolism during labour and delivery: a population-based study of 8 million births, Archives of Gynecology and Obstetrics, 289, 275-284, 2014	Reports combined adjusted data for pregnancy- and postpartum-related VTE risk. No relevant data.
Abdalla, A. A., Muddathir, A. R. M., Elamin, E. M., The role of factor V Leiden 1691G>A and prothrombin 20210G>A mutations in hypercoagulable state associated with venous thromboembolism among sudanese patients, International Journal of Laboratory Hematology, 39 (Supplement 2), 3, 2017	Conference abstract
Abdul Sultan, A., Tata, L. J., Grainge, M. J., West, J., The Incidence of First Venous Thromboembolism in and around Pregnancy Using Linked Primary and Secondary Care Data: A Population Based Cohort Study from England and Comparative Meta-Analysis, PLoS ONE, 8 (7) (no pagination), 2013	Meta-Analysis: references checked no additional relevant studies identified
Abdul Sultan, A., West, J., Tata, L., Fleming, K., Nelson-Piercy, C., Grainge, M., The risk of venous thromboembolism in and around pregnancy: A populationbased cohort study, Journal of Perinatal Medicine. Conference: 10th World Congress of Perinatal Medicine, 39, 2011	Conference abstract: No relevant data
Abou-Nassar, K., Kovacs, M. J., Kahn, S. R., Wells, P., Doucette, S., Ramsay, T., Clement, A. M., Khurana, R., MacKinnon, K., Blostein, M., Solymoss, S., Kingdom, J., Sermer, M., Rey, E., Rodger, M., The effect of dalteparin on coagulation activation during pregnancy in women with thrombophilia. A randomized trial, Thrombosis and Haemostasis, 98, 163-171, 2007	No relevant study design/data
Adachi, T., Hashiguchi, K., Arai, Y., Ohta, H., Clinical study of venous thromboembolism during pregnancy and puerperium, Seminars in Thrombosis and Hemostasis, 27, 149-154, 2001	No relevant study design/data

Study	Reason for exclusion
al Zahrani, H., Gari, M., Sejeni, S., Pattern of deep venous thrombosis in Jeddah area, western Saudi Arabia, International AngiologyInt Angiol, 12, 54-8, 1993	No relevant study design
Alessio, A. M., Hoehr, N. F., Siqueira, L. H., Ozelo, M. C., de Padua Mansur, A., Annichino-Bizzacchi, J. M., Association between estrogen receptor alpha and beta gene polymorphisms and deep vein thrombosis, Thrombosis Research, 120, 639-645, 2007	No relevant study design
Al-Gahtani,F.H., Pregnancy-associated venous thromboembolism: Part I - Deep vein thrombus diagnosis and treatment, Saudi Medical Journal, 30, 13-23, 2009	Non-systematic Review
Alguel, G., Vormittag, R., Simanek, R., Kyrle, P. A., Quehenberger, P., Mannhalter, C., Husslein, P., Pabinger, I., Preeclampsia and pregnancy loss in women with a history of venous thromboembolism and prophylactic low-molecular-weight heparin (LMWH) during pregnancy, Thrombosis & Haemostasis, 96, 285-9, 2006	No relevant study design
Alsayegh, F., Al-Jassar, W., Wani, S., Tahlak, M., Al-Bahar, A., Al-Kharusi, L., Al-Tamimi, H., El-Taher, F., Mahmood, N., Al-Zakwani, I., Venous thromboembolism risk and adequacy of prophylaxis in high risk pregnancy in the Arabian Gulf, Current Vascular Pharmacology, 14, 368-373, 2016	No relevant study design/data
Alsheef, M. A., Alabbad, A. M., Albassam, R. A., Alarfaj, R. M., Pregnancy and venous thromboembolism: A case series analysis of clinical presentation, diagnosis, thrombophilia, treatment and outcome, Thrombosis Research, 151 (Supplement 1), S133, 2017	Conference abstract: No relevant data
Alsheef, M. A., Alabbad, A. M., Albassam, R. A., Alarfaj, R. M., Alarfaj, O. A., Case control study of the predictors of pregnancy-induced venous thromboembolism among Saudi pregnant women, Thrombosis Research, 151 (Supplement 1), S108, 2017	Conference abstract: No relevant data
Anderson, F. A., Jr., Spencer, F. A., Risk factors for venous thromboembolism, Circulation, 107, I-9, 2003	Non-systematic Review
Armstrong, E. M., Bellone, J. M., Hornsby, L. B., Treadway, S., Phillippe, H. M., Pregnancy-related venous thromboembolism, Journal of Pharmacy Practice, 27, 243-252, 2014	Non-systematic Review
Bahl, V., Hu, H. M., Henke, P. K., Wakefield, T. W., Campbell Jr, D. A., Caprini, J. A., A validation study of a retrospective venous thromboembolism risk scoring method, Annals of Surgery, 251, 344-350, 2010	Validation study of VTE risk scoring in non-pregnant population - no relevant study data
Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C. M., Koopman, M. M. W.,	Retrospective cohort study examining frequency of pregnancy-related VTE in antithrombin,

Study	Reason for exclusion
Hamulyak, K., Prim, M. H., Van Der Meer, J., Buller, H. R., Prothrombin 20210A mutation: A mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study, Archives of Internal Medicine, 164, 1932-1937, 2004	protein C or protein S deficient and non-deficient women - no relevant data
Bates, S. M., Pregnancy-Associated Venous Thromboembolism: Prevention and Treatment, Seminars in Hematology, 48, 271-284, 2011	Non-systematic review
Bauersachs, R. M., Dudenhausen, J., Faridi, A., Fischer, T., Fung, S., Geisen, U., Harenberg, J., Herchenhan, E., Keller, F., Kemkes-Matthes, B., Schinzel, H., Spannagl, M., Thaler, C. J., Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women, Thrombosis and Haemostasis, 98, 1237-1245, 2007	Examines 3 pregnancy-VTE management strategies - no relevant data
Berens, C., Esser, A., Nadal, J., Oldenburg, J., Potzsch, B., Ruhl, H., Assessment of peripartum management in a population at high risk for venous thromboembolism, Research and Practice in Thrombosis and Haemostasis, 1 (Supplement 1), 1019-1020, 2017	Conference abstract - no relevant data
Bergrem, A., Dahm, A. E. A., Jacobsen, A. F., Sandvik, L., Sandset, P. M., Differential haemostatic risk factors for pregnancy-related deep-vein thrombosis and pulmonary embolism: A population-based case-control study, Thrombosis and Haemostasis, 108, 1165-1171, 2012	Non-nested case control study - no relevant study design
Bergrem, A., Dahm, A. E. A., Jacobsen, A. F., Sandvik, L., Sandset, P. M., Differential risk factors for pregnancy-related deep vein thrombosis and pulmonary embolism-Results froma population-based case-control study, Thrombosis Research, 1), S75, 2013	Conference abstract - no relevant data
Bergrem, A., Jacobsen, E. M., Skjeldestad, F. E., Jacobsen, A. F., Skogstad, M., Sandset, P. M., The association of antiphospholipid antibodies with pregnancy-related first time venous thrombosis--a population-based case-control study, Thrombosis Research, 125, e222-7, 2010	Non-nested case control study - no relevant study design
Bhakuni, T., Sharma, A., Mahapatra, M., Saxena, R., Aman Jairajpuri, M., Assessment of various thrombophilic risk factors and rs2227589 in Indian RPL population, Thrombosis Research, 3), S107, 2014	Conference abstract - no relevant data
Biino, G., Portas, L., Murgia, F., Vaccargiu, S., Parracciani, D., Pirastu, M., Balduini, C. L., A population-based study of an Italian genetic isolate reveals that mean platelet volume is not a risk factor for thrombosis, Thrombosis Research, 129, e8-e13, 2012	Cross-sectional study - no relevant data

Study	Reason for exclusion
Biron-Andreani, C., Schved, J. F., Daures, J. P., Factor V Leiden mutation and pregnancy-related venous thromboembolism: What is the exact risk? results from a meta-analysis, Thrombosis and Haemostasis, 96, 14-18, 2006	Systematic review - all references checked, no additional relevant articles
Blanco-Molina, A., Trujillo-Santos, J., Criado, J., Gutierrez, R., Alvarez, J. C., Gutierrez, M. R., Otero, R., Arcelus, J. I., Casado, I., Barron, M., Buges, J., Epelde, F., Monreal, M., Raguer, E., Raventos, A., Tolosa, C., Barba, R., Del Toro, J., Fernandez-Capitan, C., Gutierrez, J., Jimenez, D., Pedrajas, J. M., Randon, P., Ruiz-Gimenez, N., Blanco, A., Lopez, L., Tirado, R., Cabezudo, M. A., Lopez, I., Conget, F., Gabriel, F., Grau, E., Lopez, G., Naufall, M. D., Roman, P., Todoli, J. A., Gallego, P., Soto, M. J., Garcia-Bragado, F., Soler, S., Guijarro, R., Guil, M., Martin, J. J., Hernandez, L., Maestre, A., Sanchez, R., Lecumberri, R., Orue, M. T., Samperiz, A. L., Tiberio, G., Herrera, S., Page, M. A., Trujillo, J., Lobo, J. L., Montes, J., Nunez, M. J., Nieto, J. A., Portillo, J., Rabunal, R., Sanchez, J. F., Torre, J. A., Vasco, B., Uresandi, F., Valle, R., Guillot, K., Mismetti, P., Llobet, X., Venous thromboembolism during pregnancy or postpartum: Findings form the RIETE Registry, Thrombosis and Haemostasis, 97, 186-190, 2007	Study used only unadjusted analysis.
Bleau, N., Patenaude, V., Abenhaim, H. A., Risk of Venous Thromboembolic Events in Pregnant Patients With Autoimmune Diseases: A Population-Based Study, Clinical & Applied Thrombosis/Hemostasis, 22, 285-91, 2016	No relevant data.
Bleau, N., Patenaude, V., Abenhaim, H. A., Risk of venous thrombo-embolic events in pregnant patients with cancer, Journal of Maternal-Fetal and Neonatal Medicine, 29, 380-384, 2016	No relevant data.
Blondon, M., Casini, A., Hoppe, K. K., Boehlen, F., Righini, M., Smith, N. L., Risks of Venous Thromboembolism After Cesarean Sections: A Meta-Analysis, ChestChest, 150, 572-96, 2016	Systematic review/meta-analysis on risk of postpartum VTE - no relevant data
Blondon, M., Harrington, L. B., Boehlen, F., Robert-Ebadi, H., Righini, M., Smith, N. L., Pre-pregnancy BMI, delivery BMI, gestational weight gain and the risk of postpartum venous thrombosis, Thrombosis Research, 145, 151-156, 2016	Examines risk of postpartum VTE no - relevant data
Blondon, M., Quon, B. S., Harrington, L. B., Bounameaux, H., Smith, N. L., Association between newborn birth weight and the risk of postpartum maternal venous thromboembolism a population-based case-control study, Circulation, 131, 1471-1476, 2015	Examines risk of postpartum VTE no - relevant data
Blondon,M., Harrington,L.B., Righini,M., Boehlen,F., Bounameaux,H., Smith,N.L., Racial and ethnic differences in the risk of postpartum	Examines risk of postpartum VTE no - relevant data

Study	Reason for exclusion
venous thromboembolism: A population-based, case-control study, Journal of Thrombosis and Haemostasis, 12, 2002-2009, 2014	
Brill-Edwards, P., Ginsberg, J. S., Gent, M., Hirsh, J., Burrows, R., Kearon, C., Geerts, W., Kovacs, M., Weitz, J. I., Robinson, K. S., Whittom, R., Couture, G., Safety of withholding heparin in pregnant women with a history of venous thromboembolism, New England Journal of Medicine, 343, 1439-1444, 2000	Prospective cohort study - no relevant adjusted data reported
Broms, G., Linder, M., Granath, F., Elmberg, M., Stephansson, O., Kieler, H., Inflammatory bowel disease in pregnancy and thrombophilic disorders-impact of type of disease and treatment, Pharmacoepidemiology and Drug Safety, 3), 15, 2012	Conference abstract - no relevant data
Carr, M. H., Towers, C. V., Eastenson, A. R., Pircon, R. A., Iriye, B. K., Adashek, J. A., Prolonged bedrest during pregnancy: Does the risk of deep vein thrombosis warrant the use of routine heparin prophylaxis?, Journal of Maternal-Fetal Medicine, 6, 264-267, 1997	Retrospective cohort study - no relevant data
Chan,N., Merriman,E., Hyder,S., Woulfe,T., Tran,H., Chunilal,S., How do we manage venous thromboembolism in pregnancy? A retrospective review of the practice of diagnosing and managing pregnancy-related venous thromboembolism at two major hospitals in Australia and New Zealand, Internal Medicine Journal, 42, 1104-1112, 2012	Retrospective epidemiological chart review of pregnancy-related VTE in 2 hospitals - no relevant data
Chandrarajan, Lojana, Nelson-Piercy, Catherine, Risk of venous thromboembolism during pregnancy and birth, British Journal of Midwifery, 23, 618-622, 2015	Clinical practice article - no relevant data
Chunilal,S.D., Bates,S.M., Venous thromboembolism in pregnancy: Diagnosis, management and prevention, Thrombosis and Haemostasis, 101, 428-438, 2009	Non-systematic Review
Chunilal,S.D., Chan,W.S., Critical illness in obstetric patients: Venous thromboembolism in pregnancy, Current Women's Health Reviews, 7, 189-202, 2011	Literature review: references checked and no additional studies identified.
Clark, P., Sattar, N., Walker, I. D., Greer, I. A., The Glasgow Outcome, APCR and Lipid (GOAL) pregnancy study: Significance of pregnancy associated activated protein C resistance, Thrombosis and Haemostasis, 85, 30-35, 2001	Examines association between APC:SR sensitivity ratio and pregnancy outcomes - no relevant data
Cochery-Nouvellon, E., Mercier, E., Lissalde-Lavigne, G., Daures, J. P., Quere, I., Dauzat, M., Mares, P., Gris, J. C., Homozygosity for the C46T polymorphism of the F12 gene is a risk factor for venous thrombosis during the first pregnancy, Journal of Thrombosis and Haemostasis, 5, 700-707, 2007	Reports combined adjusted data for pregnancy- and postpartum-related VTE risk- No relevant data.

Study	Reason for exclusion
Corosu, R., Vizzaccaro, F., Moretti, S., Thrombophilic risk in pregnancy, Italian Journal of Gynaecology and Obstetrics, 10, 160-162, 1998	Non-nested case control study - no relevant study design/data
Coulam,C.B., Wallis,D., Weinstein,J., DasGupta,D.S., Jeyendran,R.S., Comparison of thrombophilic gene mutations among patients experiencing recurrent miscarriage and deep vein thrombosis, American Journal of Reproductive Immunology, 60, 426-431, 2008	Genetic association study - no relevant data
Croles, F. N., Nasserinejad, K., Duvekot, J. J., Kruip, M. J., Meijer, K., Leebeek, F. W., Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis, BMJBmj, 359, j4452, 2017	Systematic review/meta-analysis - all references checked, no additional relevant articles
Cushman,M., Glynn,R.J., Goldhaber,S.Z., Moll,S., Bauer,K.A., Deitcher,S., Shrivastava,S., Ridker,P.M., Hormonal factors and risk of recurrent venous thrombosis: The Prevention of Recurrent Venous Thromboembolism trial, Journal of Thrombosis and Haemostasis, 4, 2199-2203, 2006	RCT on thromboprophylactic treatment - no relevant study design/data
Dahm, A. E. A., Bezemer, I. D., Bergrem, A., Jacobsen, A. F., Jacobsen, E. M., Skretting, G., Rosendaal, F. R., Sandset, P. M., Candidate gene polymorphisms and the risk for pregnancy-related venous thrombosis, British Journal of Haematology, 157, 753-761, 2012	Non-nested case control study - no relevant study design
Dahm, A. E. A., Tiscia, G., Holmgren, A., Jacobsen, A. F., Skretting, G., Grandone, E., Sandset, P. M., Genetic variations in the annexin A5 gene and the risk of pregnancy-related venous thrombosis, Journal of Thrombosis and Haemostasis, 13, 409-413, 2015	Non-nested case control study - no relevant study design
Danilenko-Dixon, D. R., Heit, J. A., Silverstein, M. D., Yawn, B. P., Petterson, T. M., Lohse, C. M., Melton, Iii L. J., Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: A population-based, case-control study, American Journal of Obstetrics and Gynecology, 184, 104-110, 2001	Nested case control study - reports combined adjusted data for pregnancy- and postpartum-related VTE risk
de Andrade, M., Armasu, S. M., McCauley, B. M., Petterson, T. M., Heit, J. A., Identification of genetic interaction with risk factors using a time-to-event model, International Journal of Environmental Research and Public Health, 14 (10) (no pagination), 2017	A single centre cohort study. Not a relevant study design.
Dilley, A., Austin, H., El-Jamil, M., Hooper, W. C., Barnhart, E., Evatt, B. L., Sullivan, P. S., Ellingsen, D., Patterson-Barnett, A., Eller, D., Randall, H., Phillipp, C., Genetic factors associated with thrombosis in pregnancy in a United States population, American Journal of	Non-nested case control study - no relevant study design

Study	Reason for exclusion
Obstetrics and Gynecology, 183, 1271-1277, 2000	
Dindagur, N., Kruthika-Vinod, T. P., Christopher, R., Factor V gene A4070G mutation and the risk of cerebral veno-sinus thrombosis occurring during puerperium, Thrombosis Research, 119, 497-500, 2007	Genetic association study examining risk factors for puerperal VTE - no relevant data
Dizon-Townson, D., Miller, C., Sibai, B., Spong, C. Y., Thom, E., Wendel Jr, G., Wenstrom, K., Samuels, P., Cotroneo, M. A., Moawad, A., Sorokin, Y., Meis, P., Miodovnik, M., O'Sullivan, M. J., Conway, D., Wapner, R. J., Gabbe, S. G., The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus, Obstetrics and Gynecology, 106, 517-524, 2005	Cohort study: no relevant data
Dudding, T. E., Attia, J., The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: A meta-analysis, Thrombosis and Haemostasis, 91, 700-711, 2004	Systematic review/meta-analysis of association between favor V Leiden and adverse pregnancy outcomes - no relevant data
Dutra, Caroline Gross, Fraga, Lucas Rosa, Nácul, Andréa Prestes, Passos, Eduardo Pandolfi, Gonçalves, Rozana Oliveira, Nunes, Olívia Lucia, Godoy, Bibiane Armiliato De, Leistner-Segal, Sandra, Vianna, Fernanda Sales Luiz, Schüler-Faccini, Lavínia, Sanseverino, Maria Teresa Vieira, Lack of association between thrombophilic gene variants and recurrent pregnancy loss, Human Fertility, 17, 99-105, 2014	Genetic association study examining association between thrombophilia-related genes and recurrent pregnancy loss - no relevant data
Eichinger, S., Evers, J. L. H., Glasier, A., La Vecchia, C., Martinelli, I., Skouby, S., Somigliana, E., Baird, D. T., Benagiano, G., Crosignani, P. G., Gianaroli, L., Negri, E., Volpe, A., Venous thromboembolism in women: A specific reproductive health risk, Human Reproduction Update, 19, 471-482, 2013	Non-systematic review
Ellis-Kahana, J., Sparks, A. D., Gimovsky, A. C., James, A. H., Ahmadzia, H. K., Developing a model for predicting venous thromboembolism in obese pregnant women in a national study, Thrombosis Research, 191, 42-49, 2020	Only reports on VTE occurring intra-/postpartum
Erekson, E. A., Brousseau, E. C., Dick-Biascoechea, M. A., Ciarleglio, M. M., Lockwood, C. J., Pettker, C. M., Maternal postoperative complications after nonobstetric antenatal surgery, J Matern Fetal Neonatal MedThe journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet, 25, 2639-44, 2012	Retrospective epidemiological chart review of complications following non-obstetric antenatal surgery - no relevant data
Finazzi, G., Brancaccio, V., Moia, M., Ciavarella, N., Mazzucconi, M. G., Schinco, P. C., Ruggeri, M., Pogliani, E. M., Gamba, G., Rossi, E.,	Prospective cohort study examining risk factors for VTE in pregnant and non-pregnant women - no relevant data

Study	Reason for exclusion
Baudo, F., Manotti, C., D'Angelo, A., Palareti, G., De Stefano, V., Berrettini, M., Barbui, T., Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: A four-year prospective study from the Italian registry, American Journal of Medicine, 100, 530-536, 1996	
Folkeringa, N., Brouwer, J. L. P., Korteweg, F. J., Veeger, N. J. G. M., Erwich, J. J. H. M., Van Der Meer, J., High risk of pregnancy-related venous thromboembolism in women with multiple thrombophilic defects, British Journal of Haematology, 138, 110-116, 2007	Prospective family cohort study - no relevant data
Friederich, P. W., Sanson, B. J., Simioni, P., Zanardi, S., Huisman, M. V., Kindt, I., Prandoni, P., Buller, H. R., Girolami, A., Prins, M. H., Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: Implications for prophylaxis, Annals of Internal Medicine, 125, 955-960, 1996	Retrospective cohort study examining frequency of pregnancy-related VTE in antithrombin, protein C or protein S deficient and non-deficient women - no relevant data.
Galambosi, P. J., Gissler, M., Kaaja, R. J., Ulander, V. M., Incidence and risk factors of venous thromboembolism during postpartum period: a population-based cohort-study, Acta Obstetricia et Gynecologica Scandinavica, 96, 852-861, 2017	Risk factors study for postpartum VTE - no relevant data
Gerhardt, A., Scharf, R. E., Beckmann, M. W., Struve, S., Bender, H. G., Pillny, M., Sandmann, W., Zotz, R. B., Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium, New England Journal of Medicine, 342, 374-80, 2000	Non-nested case control study - no relevant study design/data
Gerhardt, A., Scharf, R. E., Greer, I. A., Zotz, R. B., Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium, Blood, 128, 2343-2349, 2016	Non-nested case control study - no relevant study design/data
Gerhardt, A., Scharf, R. E., Zotz, R. B., Effect of hemostatic risk factors on the individual probability of thrombosis during pregnancy and the puerperium, Thrombosis and Haemostasis, 90, 77-85, 2003	Non-nested case control study - no relevant study design
Gherman, R. B., Goodwin, T. M., Leung, B., Byrne, J. D., Hethumumi, R., Montoro, M., Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy, Obstetrics and Gynecology, 94, 730-734, 1999	Retrospective chart review - no relevant study design/data
Grandone, E., Margaglione, M., Colaizzo, D., D'Andrea, G., Cappucci, G., Brancaccio, V., Di Minno, G., Genetic susceptibility to pregnancy-related venous thromboembolism: Roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations, American Journal of Obstetrics and Gynecology, 179, 1324-1328, 1998	Non-nested case control study - no relevant study design

Study	Reason for exclusion
Hammerova, L., Chabada, J., Drobny, J., Batorova, A., Factor V Leiden mutation and its impact on pregnancy complications, Acta medica (Hradec Kralove) / Universitas Carolina, Facultas Medica Hradec Kralove, 54, 117-121, 2011	Prospective cohort study - no relevant data
Hansen, A. T., Juul, S., Knudsen, U. B., Hvas, A. M., Low risk of venous thromboembolism following early pregnancy loss in pregnancies conceived by IVF, Human Reproduction, 33, 1968-1972, 2018	Prospective cohort study examining association between VTE and early pregnancy loss - no relevant data
Hansen, A. T., Kesmodel, U. S., Juul, S., Hvas, A. M., Increased venous thrombosis incidence in pregnancies after in vitro fertilization, Human Reproduction, 29, 611-7, 2014	Epidemiological retrospective cohort study - no relevant data.
Hansen, A. T., Kesmodel, U. S., Juul, S., Hvas, A. M., No evidence that assisted reproduction increases the risk of thrombosis: A Danish National cohort study, Human Reproduction, 27, 1499-1503, 2012	Epidemiological retrospective cohort study - no relevant data
Heit, J. A., Sobell, J. L., Li, H., Sommer, S. S., The incidence of venous thromboembolism among Factor V Leiden carriers: A community-based cohort study, Journal of Thrombosis and Haemostasis, 3, 305-311, 2005	Retrospective cohort study examining frequency of pregnancy-related VTE in antithrombin, protein C or protein S deficient and non-deficient women - no relevant data
Hezelgrave, N. L., Whitty, C. J. M., Shennan, A. H., Chappell, L. C., Advising on travel during pregnancy, BMJBmj, 342 (7806) (no pagination), 2011	Non-systematic review
Hiltunen, L., Rautanen, A., Rasi, V., Kaaja, R., Kere, J., Krusius, T., Vahtera, E., Paunio, M., An unfavorable combination of factor V Leiden with age, weight, and blood group causes high risk of pregnancy-associated venous thrombosis-a population-based nested case-control study, Thrombosis Research, 119, 423-432, 2007	Reports combined adjusted data for pregnancy- and postpartum-related VTE risk- No relevant data.
Hu, W., Wang, Y., Li, J., Huang, J., Pu, Y., Jiang, Y., Xu, D., Ding, Z., Zhao, B., Luo, Q., The Predictive Value of d-Dimer Test for Venous Thromboembolism During Puerperium: A Prospective Cohort Study, Clinical & Applied Thrombosis/HemostasisClin Appl Thromb Hemost, 26, 1076029620901786, 2020	Only reports on VTE occurring intra/post-partum
Jacobsen, A. F., Dahm, A., Bergrem, A., Jacobsen, E. M., Sandset, P. M., Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210A polymorphisms, Journal of Thrombosis and Haemostasis, 8, 2443-2449, 2010	Non-nested case control study - no relevant study design
Jacobsen, A. F., Skjeldestad, F. E., Sandset, P. M., Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium-a register-based case-control study, American	Non-nested case control study - no relevant study design

Study	Reason for exclusion
Journal of Obstetrics and Gynecology, 198, 233.e1-233.e7, 2008	
Jacobsen,A.F., Skjeldestad,F.E., Sandset,P.M., Ante- and postnatal risk factors of venous thrombosis: A hospital-based case-control study, Journal of Thrombosis and Haemostasis, 6, 905-912, 2008	Non-nested case control study - no relevant study design
James, A. H., Jamison, M. G., Brancazio, L. R., Myers, E. R., Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality, American Journal of Obstetrics & Gynecology, 194, 1311-5, 2006	Multi-centre cohort study - no relevant adjusted data
James, A. H., Tapson, V. F., Goldhaber, S. Z., Thrombosis during pregnancy and the postpartum period, American Journal of Obstetrics & Gynecology, 193, 216-9, 2005	Retrospective cohort study - no relevant data
Kevane, B., Donnelly, J., D'Alton, M., Cooley, S., Preston, R. J. S., Ainle, F. N., Risk factors for pregnancy-associated venous thromboembolism: A review, Journal of Perinatal Medicine, 42, 417-425, 2014	Systematic review - references checked, additional and two relevant articles retrieved
Kjellberg, U., Van Rooijen, M., Bremme, K., Hellgren, M., Factor v Leiden mutation and pregnancy-related complications, American Journal of Obstetrics and Gynecology, 203, 469.e1-469.e8, 2010	Case cohort study - no relevant adjusted data
Knight, M., Antenatal pulmonary embolism: Risk factors, management and outcomes, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 453-461, 2008	Non-nested case control study - no relevant study design
Kobayashi, T., Nakabayashi, M., Ishikawa, M., Adachi, T., Kobashi, G., Maeda, M., Ikenoue, T., Pulmonary thromboembolism in obstetrics and gynecology increased by 6.5-fold over the past decade in Japan, Circulation Journal, 72, 753-6, 2008	Epidemiological study of VTE incidence in Japan - no relevant data
Lee, S., Czuzoj-Shulman, N., Abenhaim, H. A., Behcet's disease and pregnancy: Obstetrical and neonatal outcomes in a population-based cohort of 12 million births, Journal of Perinatal Medicine, 47, 381-387, 2019	Did not report VTE outcomes
Lensen, R., Rosendaal, F., Vandenbroucke, J., Bertina, R., Factor V Leiden: the venous thrombotic risk in thrombophilic families, British Journal of Haematology, 110, 939-45, 2000	Family genetic association study - no relevant adjusted data reported
Lenz, B., Drenjancevic, D., Zibar, D., Samardzija, M., Milostic-Srb, A., The investigation of hereditary and acquired thrombophilia risk factors in the development of complications in pregnancy in Croatian women, Journal of Maternal-Fetal and Neonatal Medicine, 29, 264-269, 2016	Genetic association study - no relevant data
Lindqvist, P. G., Torsson, J., Almqvist, A., Bjorgell, O., Postpartum thromboembolism:	Retrospective case control study on postpartum VTE risk factors - no relevant study design/data

Study	Reason for exclusion
severe events might be preventable using a new risk score model, Vascular Health & Risk Management, 4, 1081-7, 2008	
Liu, N., Vigod, S. N., Farrugia, M. M., Urquia, M. L., Ray, J. G., Venous thromboembolism after induced abortion: a population-based, propensity-score-matched cohort study in Canada, The Lancet Haematology, 5, e279-e288, 2018	Cohort study of VTE risks after abortion not during pregnancy-no relevant data
Liu, S., Rouleau, J., Joseph, K. S., Sauve, R., Liston, R. M., Young, D., Kramer, M. S., Baskett, T. F., Bartholomew, S., Fraser, W., Heaman, H., Huang, H., McCourt, M., Kinch, R. A., O'Campo, P., Pelletier, L., Epidemiology of Pregnancy-associated Venous Thromboembolism: A Population-based Study in Canada, Journal of Obstetrics and Gynaecology Canada, 31, 611-620, 2009	Retrospective cohort study - no relevant data (includes puerperal VTE)
Martinelli, I., Battaglioli, T., De Stefano, V., Tormene, D., Valdre, L., Grandone, E., Tosetto, A., Mannucci, P. M., The risk of first venous thromboembolism during pregnancy and puerperium in double heterozygotes for factor V Leiden and prothrombin G20210A, Journal of Thrombosis and Haemostasis, 6, 494-498, 2008	Retrospective family cohort study - no relevant data
Martinelli, I., De Stefano, V., Taioli, E., Paciaroni, K., Rossi, E., Mannucci, P. M., Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium, Thrombosis and Haemostasis, 87, 791-795, 2002	Non-nested case control study - no relevant study design
Mazza, J. J., Hypercoagulability and Venous Thromboembolism: A Review, Wisconsin Medical Journal, 103, 41-49, 2004	Non-systematic review
McColl, M. D., Ellison, J., Reid, F., Tait, R. C., Walker, I. D., Greer, I. A., Prothrombin 20210 G->A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy, British Journal of Obstetrics and Gynaecology, 107, 565-569, 2000	Genetic association study - no relevant data
McColl, M. D., Walker, I. D., Greer, I. A., Risk factors for venous thromboembolism in pregnancy, Current Opinion in Pulmonary Medicine, 5, 227-232, 1999	Non-systematic review
Meglic, L., Stegnar, M., Milanez, T., Bozic, M., Peterlin, B., Peternel, P., Novak-Antolic, Z., Factor V Leiden, prothrombin 20210G -> A, methylenetetrahydrofolate reductase 677C -> T and plasminogen activator inhibitor 4G/5G polymorphism in women with pregnancy-related venous thromboembolism, European Journal of Obstetrics Gynecology and Reproductive Biology, 111, 157-163, 2003	Non-nested case control study - no relevant study design
Middeldorp, S., Henkens, C. M. A., Koopman, M. M. W., Van Pampus, E. C. M., Hamulyak, K., Van Der Meer, J., Prins, M. H., Buller, H. R., The	Retrospective family cohort study - no relevant data reported

Study	Reason for exclusion
incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis, Annals of Internal Medicine, 128, 15-20, 1998	
Middeldorp, S., Meinardi, J. R., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van Der Meer, J., Prins, M. H., Buller, H. R., A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism, Annals of Internal Medicine, 135, 322-7, 2001	Prospective family cohort study - no relevant data reported
Mitic, G., Kovac, M., Jurisic, D., Djordjevic, V., Ilic, V., Salatic, I., Spasic, D., Novakov Mikic, A., Clinical characteristics and type of thrombophilia in women with pregnancy-related venous thromboembolic disease, Gynecologic & Obstetric InvestigationGynecol Obstet Invest, 72, 103-8, 2011	Epidemiological study of prevalence of thrombophilia in pregnancy-related VTE - no relevant data
Mitic, G., Povazan, L., Lazic, R., Spasic, D., Maticki-Sekulic, M., Deficiency of the natural anticoagulant proteins in women with pregnancy related venous thromboembolism, Medicinski pregled, 62, 53-62, 2009	Non-nested case control study - no relevant study design
Momot, A. P., Nikolaeva, M. G., Yasafova, N. N., Zainulina, M. S., Momot, K. A., Taranenko, I. A., Clinical and laboratory manifestations of the prothrombin gene mutation in women of reproductive age, Journal of Blood Medicine, 10, 255-263, 2019	No adjustment for confounding factors
Morris,J.M., Algert,C.S., Roberts,C.L., Incidence and risk factors for pulmonary embolism in the postpartum period, Journal of Thrombosis and Haemostasis, 8, 998-1003, 2010	Retrospective cohort study on postpartum VTE risk factors - no relevant data
Murphy,R.P., Donoghue,C., Nallen,R.J., D'Mello,M., Regan,C., Whitehead,A.S., Fitzgerald,D.J., Prospective evaluation of the risk conferred by factor V Leiden and thermolabile methylenetetrahydrofolate reductase polymorphisms in pregnancy, Arteriosclerosis, Thrombosis and Vascular Biology, 20, 266-270, 2000	Genetic association study - no relevant data
Nkoke, C., Ngueping, M. J. T., Atemkeng, F., Teuwafeu, D., Boombhi, J., Menanga, A., Incidence of venous thromboembolism, risk factors and prophylaxis in hospitalized patients in the south west region of cameroon, Vascular Health and Risk Management, 16, 317-324, 2020	Did not specifically include pregnant women
O'Connor, D. J., Scher, L. A., Gargiulo, N. J., 3rd, Jang, J., Suggs, W. D., Lipsitz, E. C., Incidence and characteristics of venous thromboembolic disease during pregnancy and the postnatal period: a contemporary series, Annals of Vascular SurgeryAnn Vasc Surg, 25, 9-14, 2011	Epidemiological retrospective chart review pregnancy-related VTE events - no relevant data

Study	Reason for exclusion
Ogunyemi, D., Cuellar, F., Ku, W., Arkel, Y., Association between inherited thrombophilias, antiphospholipid antibodies, and lipoprotein A levels and venous thromboembolism in pregnancy, American Journal of Perinatology, 20, 17-23, 2003	Epidemiological case control study - no relevant study design/data
Oppong, S. A., Torto, M., Beyuo, T., Risk factors and pregnancy outcome in women aged over 40 years at Korle-Bu Teaching Hospital in Accra, Ghana, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 149, 56-60, 2020	Non-nested case control study
Pabinger, I., Grafenhofer, H., Kaider, A., Kyrle, P. A., Quehenberger, P., Mannhalter, C., Lechner, K., Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis, Journal of Thrombosis and Haemostasis, 3, 949-954, 2005	Retrospective cohort study - no relevant adjusted data reported
Pabinger,I., Nemes,L., Rintelen,C., Koder,S., Lechler,E., Loreth,R.M., Kyrle,P.A., Scharrer,I., Sas,G., Lechner,K., Mannhalter,C., Ehrenforth,S., Pregnancy-associated risk for venous thromboembolism and pregnancy outcome in women homozygous for factor V Leiden, Hematology Journal, 1, 37-41, 2000	Genetic association case control study examining assocaition between factor V Leiden mutation and pregnancy-related VTE risk - no relevant study design/data
Pallasmaa, N., Ekblad, U., Aitokallio-Tallberg, A., Uotila, J., Raudaskoski, T., Ulander, V. M., Hurme, S., Cesarean delivery in Finland: maternal complications and obstetric risk factors, Acta Obstetricia et Gynecologica Scandinavica, 89, 896-902, 2010	Prospective cohort study examining risk factors for caesarean section-related morbidity - no relevant data
Pessione, F., De Mouzon, J., Deveaux, A., Epelboin, S., Gervoise-Boyer, M. J., Jimenez, C., Levy, R., Valentin, M., Viot, G., Bergere, M., Merlet, F., Jonveaux, P., Adverse obstetric and perinatal outcome with in vitro fertilization technology: A French nationwide population-based study, Gynecologie Obstetrique Fertilite et Senologie, 48, 351-358, 2020	Article in French
Rheaume, M., Weber, F., Durand, M., Mahone, M., Pregnancy-Related Venous Thromboembolism Risk in Asymptomatic Women With Antithrombin Deficiency: A Systematic Review, Obstetrics & GynecologyObstet Gynecol, 127, 649-56, 2016	Systematic review - references checked, no additional relevant articles reported adjusted data
Robertson, L., Wu, O., Langhorne, P., Twaddle, S., Clark, P., Lowe, G. D. O., Walker, I. D., Greaves, M., Brenkel, I., Regan, L., Greer, I. A., Thrombophilia in pregnancy: A systematic review, British Journal of Haematology, 132, 171-196, 2006	Systematic review - references checked, no additional relevant articles reported adjusted data
Robinson,H.E., O'Connell,C.M., Joseph,K.S., McLeod,N.L., Maternal outcomes in pregnancies complicated by obesity, Obstetrics and Gynecology, 106, 1357-1364, 2005	No relevant data

Study	Reason for exclusion
Samama, M. M., Simon, D., Horellou, M. H., Trossaert, M., Elalamy, I., Conard, J., Diagnosis and clinical characteristics of inherited activated protein C resistance, Haemostasis, 26 Suppl 4, 315-30, 1996	Genetic association family cohort study - no relevant data
Scheres, L. J. J., van Hylckama Vlieg, A., Ballieux, Bepb, Fauser, Bcjm, Rosendaal, F. R., Middeldorp, S., Cannegieter, S. C., Crew consortium, Endogenous sex hormones and risk of venous thromboembolism in young women, Journal of Thrombosis & HaemostasisJ Thromb Haemost, 17, 1297-1304, 2019	Not all participants were pregnant
Schwarzman, P., Paz Levy, D., Walfisch, A., Sergienko, R., Bernstein, E. H., Sheiner, E., Maternal history of recurrent pregnancy loss and long-term risk of thromboembolic events, Journal of Reproductive Immunology, 138 (no pagination), 2020	Did not report VTE during pregnancy
Shi, H., Zheng, H., Yin, Y. F., Hu, Q. Y., Teng, J. L., Sun, Y., Liu, H. L., Cheng, X. B., Ye, J. N., Su, Y. T., Wu, X. Y., Zhou, J. F., Norman, G. L., Gong, H. Y., Shi, X. M., Peng, Y. B., Wang, X. F., Yang, C. D., Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential diagnostic markers and risk predictors of venous thrombosis and obstetric complications in antiphospholipid syndrome, Clinical Chemistry & Laboratory MedicineClin Chem Lab Med, 56, 614-624, 2018	Epidemiological antibody study on VTE risk factors - no relevant population/data
Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Ten Cate, J. W., Girolami, A., Prins, M. H., Incidence of venous thromboembolism in families with inherited thrombophilia, Thrombosis and Haemostasis, 81, 198-202, 1999	Family genetic association study - no relevant adjusted data reported
Skeith, L., Carrier, M., Robinson, S. E., Alimam, S., Rodger, M. A., Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis, BloodBlood, 129, 934-939, 2017	Systematic review - references checked, no additional relevant articles
Sogaard, K. K., Horvath-Puho, E., Gronbaek, H., Jepsen, P., Vilstrup, H., Sorensen, H. T., Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study, American Journal of Gastroenterology, 104, 96-101, 2009	Retrospective non-nested case control study on VTE risk factors in patients with liver disease - no relevant population/study design
Suematsu, Y., Obi, Y., Shimomura, A., Alizadeh, R. F., Vaziri, N. D., Nguyen, N. T., Stamos, M. J., Ichii, H., Risk of Postoperative Venous Thromboembolism Among Pregnant Women, American Journal of Cardiology, 120, 479-483, 2017	Multivariate regression analysis not conducted
Sultan, A. A., Grainge, M. J., West, J., Fleming, K. M., Nelson-Piercy, C., Tata, L. J., Impact of	Retrospective cohort study of VTE in postpartum-no relevant data

Study	Reason for exclusion
risk factors on the timing of first postpartum venous thromboembolism: A population-based cohort study from England, Blood, 124, 2872-2880, 2014	
Sultan, A. A., West, J., Tata, L. J., Fleming, K. M., Nelson-Piercy, C., Grainge, M. J., Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study, Br J HaematolBritish journal of haematology, 156, 366-73, 2012	Population-based study - non-pregnant control group/no relevant data
Tam, W. H., Ng, M. H. L., Yiu, A. K. W., Lau, K. M., Cheng, G. Y. M., Li, C. Y., Thrombophilia among chinese women with venous thromboembolism during pregnancy, Gynecologic and Obstetric Investigation, 73, 183-188, 2012	Descriptive case series study - no relevant data/study design
Thurn, L., Wikman, A., Lindqvist, P. G., Postpartum blood transfusion and hemorrhage as independent risk factors for venous thromboembolism, Thrombosis Research, 165, 54-60, 2018	Retrospective cohort Study of postpartum VTE- no relevant data
Tormene, D., De Stefano, V., Grandone, E., Za, T., Perlati, M., Rossi, E., Margaglione, M., Simioni, P., The G20210A prothrombin variant and the risk of venous thromboembolism or fetal loss in pregnant women: A family study, Journal of Thrombosis and Haemostasis, 5, 2193-2196, 2007	Family cohort study no relevant data
Tormene, D., Simioni, P., Prandoni, P., Luni, S., Zerbinati, P., Sartor, D., Franz, F., Girolami, A., Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women, Haematologica, 86, 1305-1309, 2001	Single centre cohort study - no relevant study design
van Boven, H. H., Vandenbroucke, J. P., Briet, E., Rosendaal, F. R., Gene-gene and gene-environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency, Blood, 94, 2590-4, 1999	Genetic association study - no relevant data
Veselu, I. N., Boiangiu, A., Solomon, O., Filipescu, A., Vladareanu, R., Vladareanu, S., Assessment of risk factors for pulmonary embolism during pregnancy and puerpelium-management and maternal and neonatal outcomes. A literature review, Gineco.eu, 13, 40-41, 2017	Non-systematic review
Virkus, R. A., Leth Lokkegaard, E. C., Bergholt, T., Mogensen, U., Langhoff-Roos, J., Lidegaard, O., Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005; A national cohort study, Thrombosis and Haemostasis, 106, 304-309, 2011	Nested case control study - no relevant adjusted data reported
Vora,S., Ghosh,K., Shetty,S., Salvi,V., Satoskar,P., Deep venous thrombosis in the antenatal period in a large cohort of pregnancies from western India, Thrombosis Journal [Electronic Resource], 5, 9-, 2007	Non-nested case control study - no relevant study design

Study	Reason for exclusion
Vormittag, R., Pabinger, I., Thrombophilia and pregnancy complications, Hamostaseologie, 26, 59-62, 2006	Non-systematic review
Waldman, M., Sheiner, E., Sergienko, R., Shoham-Vardi, I., Can we identify risk factors during pregnancy for thrombo-embolic events during the puerperium and later in life?, Journal of Maternal-Fetal and Neonatal Medicine, 28, 1005-1009, 2015	Nested case-control study of VTE risk factors in postpartum period and after pregnancy - no relevant population/data
Wen, T., Wright, J. D., Goffman, D., D'Alton, M. E., Mack, W. J., Attenello, F. J., Friedman, A. M., Postpartum venous thromboembolism readmissions in the United States, American Journal of Obstetrics and Gynecology, 219, 401.e1-401.e14, 2018	Reported VTE readmission only and postpartum only
Won, H. S., Kim, D. Y., Yang, M. S., Lee, S. J., Shin, H. H., Park, J. B., Pregnancy-induced hypertension, but not gestational diabetes mellitus, is a risk factor for venous thromboembolism in pregnancy, Korean Circulation Journal, 41, 23-27, 2011	A single hospital based study
Yilmazer, M., Kurtay, G., Sonmezer, M., Akar, N., Factor V Leiden and prothrombin 20210 G-A mutations in controls and in patients with thromboembolic events during pregnancy or the puerperium, Archives of Gynecology & Obstetrics, 268, 304-8, 2003	Non-nested case control study - no relevant study design
Zhang, W., Shen, J., Sun, J. L., Risk scores, prevention, and treatment of maternal venous thromboembolism, World Journal of Clinical CasesWorld j, 8, 2210-2218, 2020	No adjustment for confounding factors
Zhou, Z. H., Chen, Y., Zhao, B. H., Jiang, Y., Luo, Q., Early Postpartum Venous Thromboembolism: Risk Factors and Predictive Index, Clinical and Applied Thrombosis/Hemostasis, 25, 2019	Only reported VTE postpartum
Ziakas, P. D., Poulou, L. S., Pavlou, M., Zintzaras, E., Thrombophilia and venous thromboembolism in pregnancy: a meta-analysis of genetic risk, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 191, 106-11, 2015	Systematic review/meta-analysis - all references checked, no additional relevant articles
Zotz, R. B., Gerhardt, A., Kluft, C., Scharf, R. E., Venous thromboembolism during pregnancy is not associated with persistent elevated activated protein C (APC) sensitivity ratio based on the endogenous thrombin potential, Thrombosis and Haemostasis, 93, 306-310, 2005	Non-nested case control study - no relevant study design
Zotz, R. B., Gerhardt, A., Scharf, R. E., Inherited thrombophilia and gestational venous thromboembolism, Women's Health, 3, 215-225, 2007	Non-systematic review
Zotz, R. B., Gerhardt, A., Scharf, R. E., Prediction, prevention, and treatment of venous thromboembolic disease in pregnancy,	Non-systematic review

Study	Reason for exclusion
Seminars in Thrombosis and Hemostasis, 29, 143-153, 2003	
Zuo, Y., Fan, J., Sarode, R., Zhang, S., Makris, U. E., Karp, D. R., Shen, Y. M., Identifying Additional Risk Factors for Thrombosis and Pregnancy Morbidities Among Antiphospholipid Antibodies Carriers, Clinical and Applied Thrombosis/Hemostasis, 24, 980-985, 2018	Retrospective cohort study examining aPL positive carriers - no relevant population/data
Zwart, J. J., Richters, J. M., Ory, F., De Vries, J. I. P., Bloemenkamp, K. W. M., Van Roosmalen, J., Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: A nationwide population-based study of 371 000 pregnancies, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 842-850, 2008	Prospective epidemiological nested case control study - no relevant population/data

Economic studies

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix L – Research recommendations

Research recommendations for review question: What are the risk factors for venous thromboembolism (VTE) in pregnant women?

No research recommendations were made for this review question.