No. 308, June 2014 (Replaces No. 95, September 2000)

Venous Thromboembolism and Antithrombotic Therapy in Pregnancy

This clinical practice guideline has been prepared by the VTE in Pregnancy Guideline Working Group, reviewed by Maternal Fetal Medicine and Family Physician Advisory committees, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Wee-Shian Chan, MD, Vancouver BC

Evelyne Rey, MD, Montreal QC

Nancy E. Kent, MD, Vancouver BC

VTE IN PREGNANCY GUIDELINE WORKING GROUP

Wee-Shian Chan, MD (Co-Chair), Vancouver BC

Nancy E. Kent, MD (Co-Chair), Vancouver BC

Evelyne Rey, MD (Co-Chair), Montreal QC

Thomas Corbett, MD, Edmonton AB

Michèle David, MD, Montreal QC

M. Joanne Douglas, MD, Vancouver BC

Paul S. Gibson, MD, Calgary AB

Laura Magee, MD, Vancouver BC

Marc Rodger, MD, Ottawa ON

Reginald E. Smith, Pharm D, Victoria BC

Disclosure statements have been received from all contributors.

Abstract

Objective: To present an approach, based on current evidence, for the diagnosis, treatment, and thromboprophylaxis of venous thromboembolism in pregnancy and postpartum.

Evidence: Published literature was retrieved through searches of PubMed, Medline, CINAHL, and The Cochrane Library from November 2011 to July 2013 using appropriate controlled vocabulary (e.g. pregnancy, venous thromboembolism, deep vein thrombosis, pulmonary embolism, pulmonary thrombosis) and key words (e.g., maternal morbidity, pregnancy complications, thromboprophylaxis, antithrombotic therapy). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English or French. There were no date restrictions. Grey (unpublished) literature was identified through searching the websites of clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventative Health Care (Table 1).

Key Words: Venous thromboembolism, deep vein thrombosis, pulmonary embolism, thromboprophylaxis, assisted reproductive technology, heparin, neuraxial analgesia, adverse pregnancy outcomes, pregnancy or puerperal complications

Recommendations

1. Objective testing is required following clinical suspicion of deep vein thrombosis or pulmonary embolism. (II-2A)
2. For the diagnosis of deep vein thrombosis, ultrasonography is recommended, and should be repeated at least once over 7 days if the initial study is negative. For each examination, the entire length of the venous system from the external iliac to the popliteal vein must be visualized and compression manoeuvres performed from the femoral to the popliteal vein. (II-2B)
3. For the diagnosis of pulmonary embolism, either ventilation-perfusion scan or computed tomographic angiography can be used. (II-2A) In pregnant women, a ventilation-perfusion scan is the preferred test. (III-B)
4. Neither D-dimer alone nor clinical prediction rules should be used to rule out venous thromboembolism in pregnant women without objective testing. (III-D)
5. Pregnant women diagnosed with acute venous thromboembolism should be hospitalized or followed closely as outpatients for the first 2 weeks after the initial diagnosis. (III-C)
6. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for the treatment of venous thromboembolism in pregnancy. (II-2A)
7. Heparin-induced thrombocytopenia in pregnant women is extremely rare. Consultation with a hematologist or thrombosis specialist is recommended to consider the use of heparanoids for treatment of venous thromboembolism if it occurs. (II-3B)

J Obstet Gynaecol Can 2014;36(6):527–553

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[187]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[187]

8. Vitamin K antagonists should only be considered in exceptional circumstances for the treatment of venous thromboembolism in pregnancy. (II-2A)
9. We recommend against the use of oral Xa inhibitors and oral direct thrombin inhibitors for the treatment of venous thromboembolism in pregnancy. (III-D)
10. For the treatment of acute venous thromboembolism in pregnancy we recommend adhering to the manufacturer's recommended dosing for individual low molecular weight heparins based on the woman's current weight. (II-1A) Low molecular weight heparin can be administered once or twice a day depending on the agent selected. (III-C)
11. For pregnant women initiated on therapeutic low molecular weight heparin, baseline platelet counts should be done and repeated a week later to screen for heparin-induced thrombocytopenia. (III-C)
12. For pregnant women with an acute venous thromboembolism we recommend therapeutic anticoagulation for a minimum of 3 months. (I-A)
13. Following initial treatment, anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum. (III-C)
14. In pregnant women with acute proximal leg deep vein thrombosis, the use of graded compression stockings can be considered for relief of symptoms. (III-C)
15. Thrombolytic therapy in pregnancy should only be considered in limb-threatening deep vein thrombosis or massive pulmonary embolism. (III-C)
16. Vena cava filters should only be used in pregnant women with acute pulmonary embolism or deep vein thrombosis and contraindications to anticoagulation. (III-C)
17. Computed tomographic venography and/or magnetic resonance imaging should be performed to rule out cerebral venous thrombosis if suspected. (I-C)
18. Therapeutic dose anticoagulation should be initiated for confirmed cerebral venous thrombosis. (II-2A)
19. Thromboprophylaxis should be considered in future pregnancies following a cerebral venous thrombosis. (II-1C)
20. For superficial thrombophlebitis, compression ultrasound should be performed to exclude deep vein thrombosis (II-2A), and it should be repeated if proximal extension is suspected based on worsening phlebitis. (III-C)
21. Prophylactic or intermediate dose low molecular weight heparin for 1 to 6 weeks is recommended for women with bilateral superficial thrombophlebitis, for very symptomatic women, and for superficial thrombophlebitis located ≤ 5 cm from the deep venous system (saphenofemoral and saphenopopliteal junctions) or affecting ≥ 5 cm of vein. (I-A)
22. Observation alone is recommended in women with superficial thrombophlebitis at low risk of deep vein thrombosis and for those who do not require symptom control. Clinical follow-up of these women should occur within 7 to 10 days, with a repeat compression ultrasound within one week. (I-A)
23. Computed tomography and/or magnetic resonance imaging (with or without angiography) are the definitive imaging modalities to rule out ovarian vein thrombosis. (II-2A)
24. For confirmed ovarian vein thrombosis, we recommend parenteral broad-spectrum antibiotics, continued for at least 48 hours after defervescence and clinical improvement. (II-2A) Longer antibiotic therapy is necessary for septicemia or complicated infections. (III-C)
25. For confirmed ovarian vein thrombosis, therapeutic dose anticoagulation could be considered for 1 to 3 months. (III-C)
26. Routine screening for all inherited thrombophilias in all women with a first episode of venous thromboembolism diagnosed in pregnancy is not indicated. (III-C)
27. Testing for protein S, protein C, and antithrombin deficiencies is indicated following a venous thromboembolism in pregnancy if there is a family history of these particular thrombophilias, or if thrombosis occurs in an unusual site. (III-C)

28. Testing for antiphospholipid antibodies is indicated if the results would affect the duration of anticoagulation. (III-C)
29. Individual risk assessment for venous thromboembolism should be performed prior to all pregnancies, once pregnancy is achieved, and repeated throughout pregnancy as new clinical situations arise. The woman's preferences and values should be taken into account when considering the use of antepartum thromboprophylaxis. (III-B)
30. Women at increased risk should be advised of the symptoms and signs of venous thromboembolism. (III-B)
31. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for antepartum thromboprophylaxis. (III-A) Low molecular weight heparin doses should be used as per the manufacturer's recommendation. (III-C)
32. Routine anti-Xa medication and platelet-level monitoring are not recommended when a patient is on a prophylactic dose of thromboprophylaxis. (II-2E)

ABBREVIATIONS

APLS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
ART	assisted reproductive technology
AT	antithrombin
ASA	acetylsalicylic acid
ASRA	American Society of Regional Anesthesia
BMI	body mass index
CT	computed tomography
CTA	CT angiography
CUS	compression ultrasound
CVT	cerebral venous thrombosis
DVT	deep vein thrombosis
FVL	factor V Leiden
HIT	heparin-induced thrombocytopenia
IUGR	intrauterine growth restriction
LDA	low-dose ASA
LMWH	low molecular weight heparin
MRI	magnetic resonance imaging
NSAID	non-steroidal anti-inflammatory drug
OHSS	ovarian hyperstimulation syndrome
OVT	ovarian vein thrombosis
PGM	prothrombin gene mutation 20210A
PC	protein C
PE	pulmonary embolism
PS	protein S
SGA	small for gestational age
SLE	systemic lupus erythematosus
ST	superficial thrombophlebitis
UH	unfractionated heparin
VQ	ventilation/perfusion
VTE	venous thromboembolism

33. We recommend therapeutic thromboprophylaxis during pregnancy in the following situations:
    a. long-term therapeutic anticoagulation used prior to pregnancy for a persistent indication; (III-B)
    b. personal history of multiple previous venous thromboembolism. (III-B)
34. We recommend intermediate or therapeutic thromboprophylaxis during pregnancy in the following situation:
    a. personal history of a previous venous thromboembolism and a high-risk thrombophilia (antithrombin deficiency, antiphospholipid syndrome) not previously on anticoagulation. (III-B)
35. We recommend prophylactic dose thromboprophylaxis during pregnancy in the following situations (absolute risk > 1%):
    a. personal history of a previous unprovoked venous thromboembolism; (II-2A)
    b. personal history of a previous venous thromboembolism related to oral contraceptives or pregnancy; (II-2A)
    c. personal history of a previous provoked venous thromboembolism and any low risk thrombophilia; (I-A)
    d. asymptomatic homozygous factor V Leiden; (II-2A)
    e. asymptomatic homozygous prothrombin gene mutation 20210A; (III-B)
    f. asymptomatic combined thrombophilia; (III-B)
    g. asymptomatic antithrombin deficiency; (III-B)
    h. non-obstetrical surgery during pregnancy, with the duration of thromboprophylaxis being procedure- and patient-dependent; (III-B)
    i. strict antepartum bedrest for ≥ 7 days in a woman with a body mass index of > 25 kg/m^2 at her first antenatal visit. (II-2B)
36. Antepartum thromboprophylaxis for isolated pregnancy-related risk factors is not recommended. (III-E)
37. Antepartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related risk factors where the overall absolute risk of venous thromboembolism is estimated to be > 1%, especially in women admitted to hospital for bed rest. (II-2B)
38. Routine thromboprophylaxis is not required for all women undergoing ovulation induction. (III-C)
39. If severe ovarian hyperstimulation syndrome occurs with assisted reproductive technology, we recommend thromboprophylaxis with low molecular weight heparin for at least 8 to 12 weeks after resolution of the syndrome. (III-B)
40. Thromboprophylaxis with low molecular weight heparin should be considered for any women at increased risk for venous thromboembolism undergoing assisted reproductive technology at the time of ovarian stimulation. (III-B)
41. Women who develop a venous thromboembolism in association with the use of assisted reproductive technology but who do not conceive in that cycle should be treated with therapeutic anticoagulation for a minimum of 3 months. (II-3A) Those who conceive in that assisted reproductive technology cycle should be treated as per recommendations 12 and 13 for acute venous thromboembolism in pregnancy. (I-A, III-C)
42. Women on prophylactic dose, intermediate dose, or therapeutic anticoagulation should have a discussion about options for analgesia/anaesthesia prior to delivery. (III-B)

43. Switching from thromboprophylactic low molecular weight heparin to a prophylactic dose of unfractionated heparin at term (37 weeks) may be considered to allow for more options with respect to labour analgesia. (III-L)
44. Discontinue prophylactic or intermediate dose low molecular weight heparin or unfractionated heparin upon the onset of spontaneous labour or the day prior to a planned induction of labour or Caesarean section. (II-3B)
45. A recent platelet count should be available on admission in labour or before Caesarean delivery in women who have been, or are, on anticoagulants. (III-B)
46. For women on low molecular weight heparin, neuraxial anaesthesia can be administered as a:
    a. prophylactic dose: a minimum of 10 to 12 hours after the last dose; (III-B)
    b. therapeutic dose: after 24 hours since the last dose. (III-B)
47. For women on unfractionated heparin, neuraxial anaesthesia can be administered as a:
    a. prophylactic dose (maximum 10 000 U/day): after no delay; (III-B)
    b. therapeutic intravenous infusion: at least 4 hours after stopping the infusion and when the activated partial thromboplastin time is normal; (III-B)
    c. therapeutic subcutaneous unfractionated heparin: when the activated partial thromboplastin time is normal. This may be 12 hours or longer after the last injection. (III-B)
48. Neuraxial anaesthesia must be avoided in a woman who is fully anticoagulated or in whom there is evidence of altered coagulation. (II-3A)
49. Removal of a neuraxial catheter left in situ postpartum should only be done 4, 10 to 12, or 24 hours following the administration of prophylactic dose unfractionated heparin (maximum 10 000 U/day), prophylactic low molecular weight heparin (single daily dose), or therapeutic dose low molecular weight heparin, respectively, or in the case of therapeutic unfractionated heparin, when the activated partial thromboplastin time is normal. (II-3B)
50. Prophylactic dose low molecular weight heparin (single daily dose) may be started or restarted 4 hours after neuraxial catheter removal, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)
51. Therapeutic low molecular weight heparin may be started or restarted at least 24 hours after a single injection neuraxial block and a minimum of 4 hours after neuraxial catheter removal, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)
52. Subcutaneous unfractionated heparin may be started or restarted at least 1 hour after a single injection neuraxial block, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)
53. Do not administer antiplatelet agents (acetylsalicylic acid or non-steroidal anti-inflammatory drugs) concomitantly with heparin if a neuraxial catheter is left in situ postpartum. (III-D)
54. Women on therapeutic anticoagulation who have received neuraxial anesthesia should be monitored closely for the development of a spinal hematoma. (III-B)
55. Universal postpartum thromboprophylaxis is not recommended. (III-D)
56. Assess women for increased risk of postpartum venous thromboembolism based on antepartum, intrapartum, and postpartum risk factors after every delivery and repeat as new clinical situations arise. (II-2B)
57. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for postpartum thrombo-prophylaxis. (III-A) Low molecular weight heparin doses should be used as per the manufacturer's recommendation. (III-C)
58. Pharmacologic thromboprophylaxis postpartum is recommended in the following situations:

    Any 1 of the following risk factors (each with an absolute risk of venous thromboembolism > 1%):

    a. history of any prior venous thromboembolism; (II-2A)
    b. any high-risk thrombophilia: antiphospholipid syndrome, antithrombin deficiency, homozygous factor V Leiden or prothrombin gene mutation 20210A, or combined thrombophilia; (II-2B)
    c. strict bedrest prior to delivery for 7 days or more; (II-2B)
    d. peripartum or postpartum blood loss of > 1 litre or blood product replacement, and concurrent postpartum surgery; (II-2B)
    e. peripartum/postpartum infection. (II-2B)
59. Postpartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related risk factors when the overall absolute risk is estimated to be greater than 1% drawn from the following groupings:
    a. any 2 of the following risk factors (each with an absolute risk of venous thromboembolism < 1% in isolation):
        i. body mass index ≥ 30 kg/m^2 at first antepartum visit; **(**II-2B**)**
        ii. smoking > 10 cigarettes/day antepartum; **(**II-2B**)**
        iii. preeclampsia; **(**II-2B**)**
        iv. intrauterine growth restriction; **(**II-2B**)**
        v. placenta previa; (II-2B)
        vi. emergency Caesarean section; (II–2B)
        vii. peripartum or postpartum blood loss of > 1 litre or blood product replacement; (II-2B)
        viii. any low risk thrombophilia: PC or PS deficiency, heterozygous factor V Leiden, or prothrombin gene mutation 20210A; **(**III-B**)**
        ix. maternal cardiac disease, SLE, sickle cell disease, inflammatory bowel disease, varicose veins, gestational diabetes; (III-B)
        x. preterm delivery; (III-B)
        xi. stillbirth. (III-B)
    b. Any 3 or more of the following risk factors (each with an absolute risk of venous thromboembolism < 1%):
        i. age > 35 years; (II-2B)
        ii. parity ≥ 2; (II-2B)
        iii. any assisted reproductive technology; (II-2B)
        iv. multiple pregnancy; (II-2B)
        v. placental abruption; (II-2B)
        vi. premature rupture of membranes; (II-2B)
        vii. elective Caesarean section; (II-2B)
        viii. maternal cancer. (III-B)

60. Intermittent or sequential pneumatic compression devices are alternatives in women when heparin is contraindicated postpartum. When the risk of postpartum venous thromboembolism is high they may be used in combination with low molecular weight heparin or unfractionated heparin. (III-B)
61. Women with ongoing and persistent risk factors should receive postpartum thromboprophylaxis for a minimum of 6 weeks postpartum. (II-3B)
62. Women with transient antepartum or intrapartum risk factors should receive postpartum thromboprophylaxis until discharged from hospital or up to 2 weeks postpartum. (III-C)
63. Universal screening for thrombophilias in women experiencing adverse pregnancy outcomes (severe preeclampsia, intrauterine growth restriction, stillbirth) is not indicated. (II-2D)
64. Women with recurrent miscarriage or late pregnancy loss should be screened for antiphospholipid syndrome. (I-B)
65. Low-dose acetylsalicylic acid or low-dose acetylsalicylic acid plus low molecular weight heparin is recommended in pregnancy in women with confirmed antiphospholipid syndrome. (I-C)
66. Low-dose acetylsalicylic acid plus low molecular weight heparin is not recommended for women with a history of recurrent miscarriage in the absence of confirmed antiphospholipid syndrome. (I-E)
67. Low molecular weight heparin should not be used routinely to reduce the risk of recurrent placenta-mediated complications in women with or without thrombophilia (excluding antiphospholipid syndrome). (I-C)

INTRODUCTION

This guideline summarizes the available data and the quality of the evidence to provide practical approaches to the diagnosis, management, and prevention of VTE in pregnancy. VTE remains an important cause of maternal morbidity and mortality in Canada with an overall incidence of DVT and PE of 12.1 per 10 000 and 5.4 per 10 000 pregnancies, respectively.[1] VTE occurs at a rate of 5.4 per 10 000 antepartum, 7.2 per 10 000 peripartum, and 4.3 per 10 000 pregnancies postpartum.[1] These rates are consistent with published literature from around the world.[2–4] The first and second trimesters of pregnancy convey similar risks for DVT, with a higher risk in the third trimester and the first 3 weeks postpartum.[5,6] PE occurs more commonly postpartum, decreasing in incidence after the first 6 weeks.[3,7]

This guideline sequentially reviews key components in reducing the risk VTE in pregnancy, which include accurate diagnosis and treatment of DVT and PE, antepartum thromboprophylaxis in appropriate patients, peripartum management of anticoagulants, and postpartum thromboprophylaxis, and concludes with a discussion of the use of heparin to prevent adverse pregnancy outcomes.

Making decisions about the management of individual patients can be challenging and complex. Wherever possible, this guideline attempts to summarize and organize the existing evidence that supports the recommendations, and it is meant to be complementary to other international guidelines on this topic.[8–15]

ACUTE VENOUS THROMBOEMBOLISM IN PREGNANCY

Due to hormonal influences on vascular tone and compressive effects on veins by the enlarging uterus, DVT in pregnancy generally presents in the lower extremities, with a predisposition for the left leg (70 to 80%).[16,17] In contrast to their presentation in non-pregnant patients, DVTs are often isolated to the iliac and/or femoral vein during pregnancy (61%).[18] Consequently diagnostic approaches advocated for use in non-pregnant patients require modification in pregnancy.[8]

Diagnosis of VTE in Pregnancy

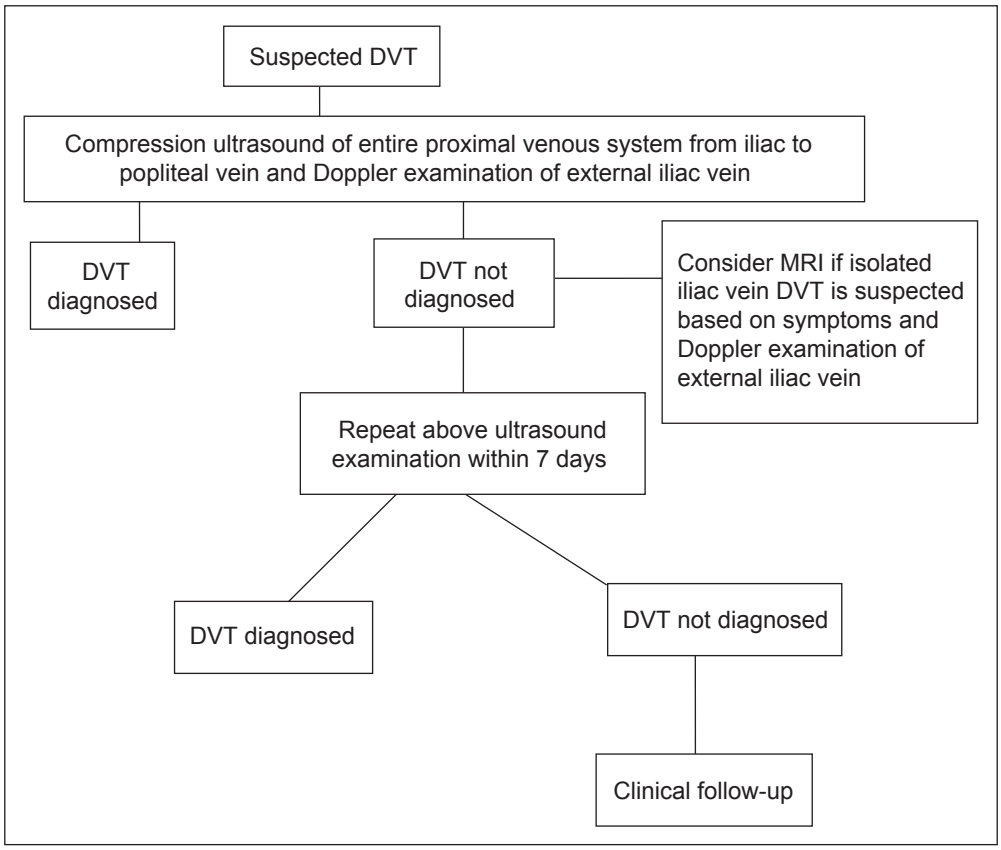
In non-pregnant patients, diagnostic approaches for VTE use a combination of validated structured clinical prediction rules with or without the use of D-dimer testing, followed by objective testing with CUS.[8] Extrapolating the same approach to pregnancy is difficult because:

1. structured prediction rules have not been validated in pregnant women,
2. the anatomic presentation of lower extremity DVT in pregnant women could affect the sensitivity of CUS,[18] and
3. current validated D-dimer level cut-off points are of limited utility.[19,20]

The potential use of a pregnancy-specific structured prediction rule and pregnancy-specific D-dimer thresholds has been reported,[21–23] but currently neither test should be used alone or in combination to diagnose or exclude VTE without further validation studies.

Our recommended diagnostic algorithm for DVT in pregnancy is shown in Figure 1. When a pregnant woman presents with a suspected DVT, she should undergo an ultrasound including direct visualization of the entire proximal venous system from the iliac to the popliteal vein.[24] Doppler studies should be performed at the level of the iliac vein to ensure that flow is present. Compression manoeuvers should be performed along the entire venous system from the femoral to the popliteal vein. The sensitivity and negative predictive value of this method are 90.9% (95% CI 69.4 to 98.4) and 98.9% (95% CI 95.5 to 99.8), respectively.[24] Published evidence is currently insufficient to support the safety of performing a single ultrasound examination in pregnant women with suspected DVT. Hence, we would recommend repeat testing with CUS and

Figure 1. Algorithm for the diagnosis of deep venous thrombosis in pregnant patients



Doppler imaging as above at least once again over the next 7 days if the initial study is negative. If isolated iliac vein obstruction (i.e. absence of flow) is suspected on Doppler examination, two options are available:

1. institute therapeutic anticoagulation followed by repeat CUS in 2 to 3 days, or
2. proceed with MRI.

The option chosen depends on patient preference, availability of expertise, and access to imaging. The specificity and sensitivity of MRI and the specific technique used to diagnose DVT in pregnancy remains uncertain.[25,26]

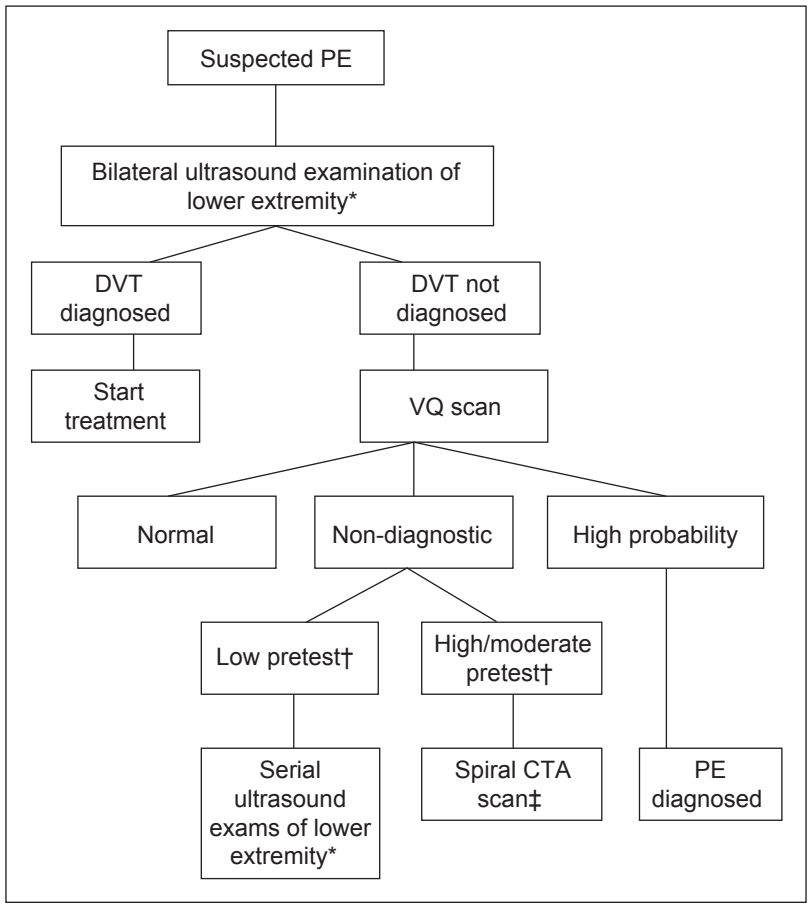
When PE is suspected clinically, definitive diagnosis requires diagnostic imaging. Several factors should be considered in the choice of VQ scan or CTA:

1. the maternal and fetal risks associated with the tests (radiation and contrast agent),
2. the sensitivity of the tests, and
3. their availability.

For both VQ scan and CTA the calculated radiation risk to the fetus is low, with levels below the threshold of 50 mGy for subsequent childhood malignancy.[27–29] The calculated minimum radiation dose to each breast for an average 60 kg woman is 20 to 35 mGy from CTA and 0.28 mGy from VQ scan.[30,31] While little is known about the long-term effects of radiation exposure to breast tissue during pregnancy, there are data linking imaging procedures to an increased risk of breast cancer.[32] The iodinated contrast agent required for computed tomographic angiography to diagnosis PE crosses the placenta and can theoretically result in fetal or neonatal hypothyroidism. However, this risk was not significant in an observational study of over 300 pregnancies.[33]

In pregnancy the observed sensitivity and negative predictive values of CTA and VQ scan appears to be high, using clinical outcome as a surrogate measure.[34–38] The specificity of a CTA in pregnancy cannot be ascertained, but studies in non-pregnant patients suggest CTA might be less specific in younger patients.[39] The decision to use CTA or VQ scan is also dictated by local availability and expertise. The CTA technique used to diagnose PE in non-pregnant patients should be modified as 5% to 36% of scans can be inadequate in pregnancy due to physiological changes.[32,40–42] We currently advocate the use of the VQ scan as the diagnostic test in pregnancy whenever possible

Figure 2. Algorithm for the diagnosis of pulmonary embolism in pregnant patients using the preferred VQ scan



*Bilateral US should include examination of the iliac veins with Doppler manoeuvers
†Pretest determined by clinician's subjective assessment
‡Modification in spiral CT protocol should be considered for pregnant patients

for the reasons listed above. However, if CTA is used, it is important to counsel patients regarding breast radiation and ensure local awareness for technique modification.

As illustrated in Figure 2, initial testing for PE should reasonably begin with bilateral CUS. Although the likelihood of asymptomatic DVT is low, if a DVT is diagnosed in the presence of unexplained chest pain, shortness of breath or tachycardia, a PE can be assumed and ventilation-perfusion scanning avoided. If CUS is negative or if the initial bilateral leg CUS examination is not available, a ventilation-perfusion scan should be performed. If the scan is normal, no further testing is needed; if the scan is high probability, anticoagulation should be initiated. For non-diagnostic scans, either CTA or serial CUS testing, based on clinical suspicion and the presence of risk factors, should be done. If CTA is selected, a negative scan will rule out a PE while a positive scan will be diagnostic. When the CTA is inconclusive or inadequate, serial whole leg ultrasound examination or repeat testing with a VQ scan is recommended.[43]

Recommendations

1. Objective testing is required following clinical suspicion of deep vein thrombosis or pulmonary embolism. (II-2A)
2. For the diagnosis of deep vein thrombosis, ultrasonography is recommended, and should be repeated at least once over 7 days if the initial study is negative. For each examination, the entire length of the venous system from the external iliac to the popliteal vein must be visualized and compression manoeuvres performed from the femoral to the popliteal vein. (II-2B)
3. For the diagnosis of pulmonary embolism, either ventilation-perfusion scan or computed tomographic angiography can be used. (II-2A) In pregnant women, a ventilation-perfusion scan is the preferred test. (III-B)
4. Neither D-dimer alone nor clinical prediction rules should be used to rule out venous thromboembolism in pregnant women without objective testing. (III-D)

Table 2. Incidence of side effects related to low molecular weight heparins in pregnancy

	Therapeutic dose	Prophylactic dose	Any dose	References
Antepartum bleeding	0% to 0.57%	0.42%	0% to 0.43%	51, 171 to 173
Postpartum bleeding	1.15% to 5.6%	0.92%	0.94% to 1.6%	51, 171 to 173
Wound hematoma	1.39%	0%	0.5% to 0.61%	51, 171 to 173
Major skin reaction/allergy	1.15%	0.96%	0.5% to 1.8%	51, 173
Osteoporosis	0%	0.26%	0.04% to 0.2%	51, 173
HIT	0%	0%	0%	51, 173

TREATMENT OF ACUTE VTE

Setting

Once an acute VTE is confirmed, therapeutic anticoagulation should be instituted promptly. There are no studies confirming the safety of outpatient management in pregnancy for women with acute VTE. Given the additional fetal concerns, pregnant women with an acute PE and/or a large proximal DVT should be considered for hospitalization or followed closely as outpatients in the initial two weeks following diagnosis if they remain hemodynamically stable.

Recommendation

5. Pregnant women diagnosed with acute venous thromboembolism should be hospitalized or followed closely as outpatients for the first 2 weeks after the initial diagnosis. (III-C)

Choice of anticoagulant

Vitamin K antagonists, such as warfarin, should not be considered for the treatment of VTE in pregnancy except in exceptional circumstances. They cross the placenta, and first trimester exposure can cause warfarin embryopathy (midfacial and limb hypoplasia, stippled bone epiphyses).[44,45] They are also associated with pregnancy loss and fetal anticoagulation at the time of delivery.[46]

UH and LMWH do not cross the placenta and do not cause teratogenicity or fetal bleeding.[47–52] HIT occurs in 3% of non-pregnant patients receiving UH. It has never been reported in a pregnancy with LMWH,[51] and outside of pregnancy HIT has been reported only in rare cases.[53]

Due to its lower side-effect profile and ease of dosing, LMWH is recommended over UH for use in pregnant women. Table 2 outlines the pooled risk estimates of side effects associated with LMWH use in pregnancy. The specific LMWH preparation used depends on availability and costs. There is no current evidence to suggest the superiority of one preparation of LMWH over another.

Danaparoid and fondaparinux are heparanoid molecules that do not cross-react with HIT antibodies. Both are treatment options for pregnant women with evidence of HIT or allergic reactions to heparins.[54,55] These agents should only be used after consultation with an appropriate specialist.

There are currently no data on the safety in pregnancy of the oral direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban and apixaban). Given their very low molecular weights, they are likely to cross the placenta and should be avoided.

Recommendations

6. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for the treatment of venous thromboembolism in pregnancy. (II-2A)
7. Heparin-induced thrombocytopenia in pregnant women is extremely rare. Consultation with a hematologist or thrombosis specialist is recommended to consider the use of heparanoids for treatment of venous thromboembolism if it occurs. (II-3B)
8. Vitamin K antagonists should only be considered in exceptional circumstances for the treatment of venous thromboembolism in pregnancy. (II-2A)
9. We recommend against the use of oral Xa inhibitors and oral direct thrombin inhibitors for the treatment of venous thromboembolism in pregnancy. (III-D)

Anticoagulant dosing and monitoring

Recommended doses for anticoagulation medications are presented in Table 3. The specific LMWH dosing is as per the manufacturer's recommendation, based on the woman's weight at the time of presentation.

Table 3. Dosing of anticoagulants

	Prophylactic dose	Intermediate dose	Therapeutic dose
UH	5000 U SC twice daily Obesity: 7500 U SC twice daily	10 000 U SC twice daily	IV: 80 U/kg bolus (max 5000 U) followed by 18 U/kg and adjusted according to local nomogram SC: 150 to 200 U/kg twice daily A lower dose should be considered in women weighing less than 50 kg[175] Target aPTT 1.5 to 2.5 × baseline
Dalteparin	5000 U SC daily or twice daily > 20 weeks Obesity: 7500 U SC daily	100 U/kg SC daily or 5000 U SC twice daily	200 U/kg daily or 100 U/kg SC twice daily
Enoxaparin	40 mg SC daily or 30 mg SC twice daily Obesity: 60 mg SC daily	40 mg SC twice daily	1 mg/kg SC twice daily or 1.5 mg/kg SC daily
Nadroparin	2850 U SC daily	Not applicable	171 U/kg SC daily
Tinzaparin	4500 U SC daily Obesity: 75 U/kg daily	4500 U SC twice daily or 9000 U SC daily	175 U/kg SC daily
Danaparoid	750 U SC twice daily	Not applicable	2000 U SC twice daily

SC: subcutaneously

There are uncertainties surrounding dosing regimens; the need for monitoring and dose increases with weight gain associated with therapeutic LMWH use in pregnancy.[56] While LMWH is administered as a single daily dose for non-pregnant patients, twice a day dosing is often used in pregnancy, especially for the first month when the risk of recurrence is greatest. This practice stems from the altered renal elimination of LMWH and the impact of weight gain, both of which affect anti-Xa activity in pregnant women.[9,14,50,52,57–59] Hence, for the treatment of acute VTE, especially major proximal VTE and PE, consideration should be given to initial monitoring of anti-Xa activity, during the first month of treatment only, to target a level of 0.6 to 1.0 U/mL 4 hours after injection, bearing in mind that target levels will vary with the LMWH used. However, the cost of the assay, the lack of correlation with clinical events, and the variability between assays makes the utility of monitoring anti-FXa activity in pregnancy controversial.[9]

If UH is selected for initial treatment, it should be administered initially as a bolus followed by a continuous infusion, using a weight-based nomogram to estimate required doses, and adjusting the infusion to keep the aPTT at 1.5 to 2.5 times baseline. After initial treatment, a switch to therapeutic subcutaneous LMWH or UH can be made. If UH is selected, it should be administered subcutaneously twice daily with doses adjusted to maintain the aPTT at 1.5 to 2.5 times pregnancy baseline at the mid-dosing interval (i.e., 6 hours after the last dose). For women with significant renal impairment (GFR < 30 mL/minute) we recommend UH over LMWH.

Recommendations

10. For the treatment of acute venous thromboembolism in pregnancy we recommend adhering to the manufacturer's recommended dosing for individual low molecular weight heparins based on the woman's current weight. (II-1A) Low molecular weight heparin can be administered once or twice a day depending on the agent selected. (III-C)
11. For pregnant women initiated on therapeutic low molecular weight heparin, baseline platelet counts should be taken and repeated a week later to screen for heparin-induced thrombocytopenia. (III-C)

Duration of therapeutic anticoagulation

If an acute VTE is diagnosed early in pregnancy, reducing the anticoagulation intensity after 3 months to intermediate or prophylactic (low) dose LMWH for the duration of the pregnancy is an option, although evidence confirming or disputing the safety of this option is unavailable. In the postpartum period, both LMWH and warfarin can be used.

Recommendations

12. For pregnant women with an acute venous thromboembolism we recommend therapeutic anticoagulation for a minimum of 3 months. (I-A)
13. Following initial treatment, anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum. (III-C)

Prevention of post-thrombotic syndrome

Post-thrombotic syndrome is a constellation of symptoms (chronic leg swelling, discoloration, pain on walking or standing) occurring in 20% to 40% of non-pregnant patients who develop a proximal DVT.[60] Graded compression stockings with 30 to 40 mmHg pressure at the ankles for 2 years were previously felt to reduce this rate.[61] A recent large placebo-controlled RCT (N = 803) showed that compression stockings did not prevent post-thrombotic syndrome, nor did they influence the severity or rate of recurrence after a first proximal DVT in an older non-pregnant population.[62] Observational studies are limited in pregnancy, therefore the need for prolonged use of graded compression stockings in pregnant women is uncertain and we recommend them for symptom relief alone.

Recommendation

14. In pregnant women with acute proximal leg deep vein thrombosis, the use of graded compression stockings can be considered for relief of symptoms. (III-C)

Thrombolytic therapy

Thrombolytic therapy has been used successfully in pregnant women who present with massive PE and hemodynamic instability.[63,64] Streptokinase, r-tPA, and urokinase do not appear to have direct placental transfer. The risk of catastrophic bleeding with their use needs to be weighed against the risk of maternal and fetal death. The only indication for thrombolytic therapy in pregnancy is limb-threatening DVT or a massive PE.[8]

Recommendation

15. Thrombolytic therapy in pregnancy should only be considered in limb-threatening deep vein thrombosis or massive pulmonary embolism. (III-C)

Vena cava filters

Vena cava filters are rarely required in pregnancy.[65–68] Placement of a retrievable filter can be considered if a patient presents with an acute PE within 2 weeks of delivery or if anticoagulation therapy has to be interrupted due to major bleeding concerns. Careful planning of filter insertion with interventional radiology is necessary to minimize fetal exposure to radiation.

Recommendation

16. Vena cava filters should only be used in pregnant women with acute pulmonary embolism or deep vein thrombosis and contraindications to anticoagulation. (III-C)

CEREBRAL VENOUS THROMBOSIS

The incidence of CVT ranges from 0.01% to 0.04% in Western countries.[69] Pregnancy and the puerperium, Caesarean section, dehydration, anemia, thrombophilia, and hypertension are identified risk factors.[69–71] Symptoms and signs include diffuse headache, altered consciousness, seizures, and focal neurological deficits. CT venography and/or MRI studies should be performed in suspected CVT if initial imaging modalities without contrast are negative or inconclusive.

Once CVT is diagnosed, therapeutic dose anticoagulation should be initiated. In addition to haematologists and thrombosis specialists, other medical and surgical subspecialists may be required depending on neurological complications.

Recommendations

17. Computed tomographic venography and/or magnetic resonance imaging should be performed to rule out cerebral venous thrombosis if suspected. (I-C)
18. Therapeutic dose anticoagulation should be initiated for confirmed cerebral venous thrombosis. (II-2A)
19. Thromboprophylaxis should be considered in future pregnancies following a cerebral venous thrombosis. (II-1C)

SUPERFICIAL THROMBOPHLEBITIS

Superficial thrombophlebitis is inflammation with or without thrombosis of a superficial vein, isolated or associated with peripheral or central catheters. The incidence in pregnancy is 0.068%.[72] ST is usually self-limiting, but it can extend into the deep venous system and/or recur. Factors associated with DVT include bilateral ST, ST presenting near the deep venous system (saphenofemoral and saphenopopliteal junctions), systemic infection, absence of varicose veins, and a previous history of DVT.[73,74] Concurrent PE is diagnosed in 4% of individuals with ST affecting ≥ 5 cm of a vein.[75]

The preferred treatment of ST is uncertain in pregnant women. A recent trial in non-pregnant patients showed that fondaparinux (2.5 mg daily for 45 days) significantly reduced the incidence of DVT and the extension and recurrence of the ST.[76] A recent Cochrane meta-analysis showed that LMWH (prophylactic and therapeutic doses) and NSAIDS for 8 to 12 days were more effective than placebo in reducing the extension or recurrence of ST, but without decreasing the occurrence of symptomatic DVT.[77] Since safety data on fondaparinux use is limited and

extended NSAID use is discouraged in pregnancy after 26 to 28 weeks' gestation, we recommend prophylactic or intermediate dose LMWH for 1 to 6 weeks in symptomatic women and in women with bilateral ST, ST of 5 cm or more, or ST located less than 5 cm from the deep venous system. Observation alone is recommended in women with ST who are at low risk of DVT and for those who do not require symptom control. Clinical follow-up of these women should occur within 7 to 10 days, with a repeat CUS within one week.

Recommendations

20. For superficial thrombophlebitis, compression ultrasound should be performed to exclude deep vein thrombosis (II-2A), and it should be repeated if proximal extension is suspected based on worsening phlebitis. (III-C)
21. Prophylactic or intermediate dose low molecular weight heparin for 1 to 6 weeks is recommended for women with bilateral superficial thrombophlebitis, for very symptomatic women, and for superficial thrombophlebitis located ≤ 5 cm from the deep venous system (saphenofemoral and saphenopopliteal junctions) or affecting ≥ 5 cm of vein. (I-A)
22. Observation alone is recommended in women with superficial thrombophlebitis at low risk of deep vein thrombosis and for those who do not require symptom control. Clinical follow-up of these women should occur within 7 to 10 days, with a repeat compression ultrasound within one week. (I-A)

OVARIAN VEIN THROMBOSIS

Ovarian vein thrombosis is an uncommon event, complicating 0.05% to 0.18% of pregnancies and affecting the right vein in up to 90% of cases.[78,79] Risk factors include Caesarean section, multiple gestation, and infection.[79] Complications include extension of the thrombus into the vena cava and/or renal veins, and sepsis. PE occurs in 13% of cases.[80] Symptoms and signs of OVT include nausea, vomiting, guarding, constant lower abdominal or flank pain, palpable sausage-shaped tender abdominal masses, fever, rigors, and leukocytosis in the first 15 days after a delivery, abortion, or ruptured ectopic pregnancy. A pelvic ultrasound should be done initially, followed by CT and/or MRI in the case of a negative or equivocal result.[81]

Broad-spectrum parenteral antibiotics should be initiated with the diagnosis of OVT and continued for at least 48 hours after defervescence and clinical improvement.[82,83] A longer treatment course is required in the presence of septicemia. Even though a small randomized study (N = 14) did not report a difference in the resolution of the fever with antibiotics alone versus antibiotics plus UH,[78] concurrent anticoagulation is often recommended.[79,82–84] We recommend anticoagulation for 1 to 3 months. There are no studies to guide the risk of recurrence of OVT and the need for thromboprophylaxis in subsequent pregnancies. The risk is likely low.[84]

Recommendations

23. Computed tomography and/or magnetic resonance imaging (with or without angiography) are the definitive imaging modalities to rule out ovarian vein thrombosis. (II-2A)
24. For confirmed ovarian vein thrombosis, we recommend parenteral broad-spectrum antibiotics, continued for at least 48 hours after defervescence and clinical improvement. (II-2A) Longer antibiotic therapy is necessary for septicemia or complicated infections. (III-C)
25. For confirmed ovarian vein thrombosis, therapeutic dose anticoagulation could be considered for 1 to 3 months. (III-C)

THROMBOPHILIA SCREENING AFTER THE DIAGNOSIS OF ACUTE VTE

There is no consensus as to whether or not patients require thrombophilia testing following the diagnosis of an acute VTE in the non-pregnant state. The acute management of the current or subsequent pregnancies is generally not altered by knowledge of the thrombophilia status, nor is counselling regarding subsequent risks of VTE. However, patients with VTE and a known family history of PS, PC, or AT deficiency would benefit from screening, as these might affect the duration of anticoagulation required for the initial episode.[85] Screening for other inherited thrombophilias is unnecessary because the presence of these will not change management.[86,87]

Screening for acquired thrombophilia, i.e. APLS, has been advocated for non-pregnant patients, since a persistently positive screen (over 12 weeks) could affect the duration of anticoagulation.[86] There are concerns about applying this to pregnant women:

1. the risk of a false positive, leading to patient anxiety, is significant,
2. the need to prolong anticoagulation beyond the usual recommended duration for pregnant patients with APLS is uncertain, and
3. repeat testing is required 8 to 12 weeks after delivery.

We therefore recommend against routine screening for APLS during pregnancy, unless thrombosis occurs in an unusual site or if the results would affect the duration of anticoagulation.

Recommendations

26. Routine screening for all inherited thrombophilias in all women with a first episode of venous thromboembolism diagnosed in pregnancy is not indicated. (III-C)
27. Testing for protein S, protein C, and antithrombin deficiencies is indicated following a venous thromboembolism in pregnancy if there is a family history of these particular thrombophilias, or if thrombosis occurs in an unusual site. (III-C)
28. Testing for antiphospholipid antibodies is indicated if the results would affect the duration of anticoagulation. (III-C)

MANAGEMENT OF ANTICOAGULATION THERAPY IN PREGNANT WOMEN WITH MECHANICAL HEART VALVES

For management of anticoagulation therapy in these patients, we would refer clinicians to the guidelines published by American College of Chest Physicians.[9]

ANTEPARTUM THROMBOPROPHYLAXIS

Recognizing that the pregnant state confers an increased risk for VTE is only the first step in determining which women will benefit from thromboprophylaxis during pregnancy. Although there is a 10-fold increase over baseline, the absolute risk of VTE during pregnancy remains low (0.5 per 1000 pregnancies),[1] and LMWH is not a risk-free medication (see Table 2). Hence, the difficulty in clinical practice is reconciling the low absolute risk of VTE with the low risk of side effects associated with thromboprophylaxis.

Determining a reasonable level of absolute risk of VTE for recommending a need for thromboprophylaxis was the first step in the development of this guideline. Most experts would agree that pregnant women with an estimated absolute risk of VTE above 10% should receive thromboprophylaxis, while those with an estimated VTE risk of less than 1% might not. When the risk falls between 1% and 10% the decision to offer thromboprophylaxis would depend on the magnitude of VTE risk, the consequences of having a DVT or PE, the risks associated with thromboprophylaxis, and the patient's and physician's preferences.[88] In this guideline we leaned towards the avoidance of VTE during pregnancy, while minimizing the number of women who would experience heparin side effects. Hence, we recommend antepartum thromboprophylaxis when the overall estimated absolute risk of VTE is greater than 1%.

Unfortunately, the magnitude to which additional biological factors in the antepartum period increase the risk for a given patient is imprecisely reported in the literature (see Table 4). Involvement of appropriate specialists should be considered in cases of clinical uncertainty.

Previous objectively documented VTEs which were unprovoked or related to hormonal therapy or pregnancy confer the highest risk of recurrence during pregnancy and warrant antepartum thromboprophylaxis.[89–92] Unprovoked or idiopathic VTEs are those occurring in the absence of clinical risk factors such as surgery, hospitalization or plaster cast immobilization within one month, and cancer.

Thrombophilias, whether inherited or acquired, have varying propensities for VTE. High-risk thrombophilias include AT deficiency, APLS, homozygous FVL or PGM, and combined thrombophilias.[93,94] The more prevalent inherited thrombophilias, such as heterozygote FVL and PGM, confer a lower risk of VTE than the rarer ones, such as PS and PC deficiency.[95,96] Since data to guide the use of thromboprophylaxis in uncommon asymptomatic thrombophilia are sparse, our recommendations for these conditions are based on estimated absolute risks for VTE in the general population[97–99] rather than on data from retrospective family studies,[100–103] especially for PC deficiency. Note that a recent task force on APLS recommended the use of hydroxychloroquine for thromboprophylaxis in patients with both SLE and APLS,[104] although the benefit of this recommendation has not been proven in pregnancy.

Screening for thrombophilia in women with a previous VTE should only be done if the result will modify management in the current pregnancy, in the presence of a family history of a high-risk inherited thrombophilia, and if the woman is fully counselled about the implications of a positive result prior to testing. Screening specifically for APLS should be considered in women with a previous unprovoked VTE or VTEs in unusual sites.

A family history of VTE alone, in the absence of a personal history or other risk factors for VTE, does not increase the personal risk of VTE sufficiently to warrant antepartum thromboprophylaxis.[105]

The contribution of various clinical and pregnancy-related risk factors for VTE has been derived from several population-based observational studies.[2,3,106–108] (Table 5)

Table 4. Literature review of incidence of symptomatic VTE antepartum without prophylaxis according to various biological and clinical risk factors

	Incidence of symptomatic VTE*			
	< 1%	1% to 5%	> 5% to 10%	> 10%
Personal history of previous VTE				
Single unprovoked		••[91,92]	•[89]	
Pregnancy-related		•[92]	•[91]	
OCP-related		•[92]	•[91]	•[90]
Single provoked (Other than OCP- or pregnancy-related)	•[91]	••[89,90]		
FVL (hetero- and homozygosity)	•[100]	•[89]		
FVL homozygosity		•[100]		
Combined FVL and PGM heterozygosity				•[94]
AT deficiency				••[176,177]
Asymptomatic thrombophilia				
FVL homozygosity		••••[101,178,181,182]	•••[96,98,179]	
PGM homozygosity				•[96]
Combined FVL and PGM heterozygosity	••[98,182]	•••[94,96,179]		
AT deficiency	••[179,183]	••[99,174]	••[98,103]	••[177,183]
FVL heterozygosity	•••••••[96–99,178–180]			
PGM heterozygosity	••••[96,98,101,179]	•[94]		
PC deficiency	•••[98,99,179]	••[102,185]	••[176,183]	
PS deficiency	•••[103,183,185]		•[176]	
Family history of symptomatic thrombophilia and unknown status				
FVL	•••[97,101,178]			
PGM	••[102,184]			
PC deficiency	••[99,103]			
PS deficiency	•••[103,183,185]			
Combined pregnancy-related risk factors				
Strict bed rest ≥ 7 days + BMI ≥ 25 kg/m^2 at first antenatal visit			•[109]	

OCP: oral contraceptive pill

*Each dot represents one study; the superscript numerals are references to those studies.

However, a large case–control study of 613 232 births with 559 cases of antepartum and postpartum VTE (overall incidence of 1/1000 live births) showed that most previously identified pregnancy-related risk factors in isolation did not increase the absolute risk of antepartum VTE above 1%.[109] This has recently been supported by a large population-based cohort study from the UK.[4] For example, although maternal obesity has been identified as a risk factor, the absolute risk of VTE associated with maternal obesity alone would not warrant the use of thromboprophylaxis, even accounting for various definitions of increased BMI presented in the literature.[107,110] Notably, the combination of antenatal bedrest for ≥ 7 days (defined as > 90% of the time in bed) and a booking (first antenatal visit) BMI of ≥ 25 kg/m^2 increased the risk of antenatal VTE to approximately 6% in the large case–control study,[109] warranting antepartum thromboprophylaxis with this combination of clinical factors (see Table 4). While we recognize that strict bedrest is rarely indicated in hospitalized obstetrical patients today, the significant increase in risk of VTE incurred when it is instituted cannot be overemphasized. Hence, antepartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related risk factors when the overall absolute risk of VTE is estimated to be greater than 1%, especially in patients who are in hospital, where bedrest is often prescribed.

Due to its lower side-effect profile, LMWH is the preferred pharmacologic agent over UH for antepartum thromboprophylaxis. Table 3 presents the doses of

Table 5. Literature review of incidence of symptomatic VTE antepartum without prophylaxis according to various clinical or pregnancy-related risk factors

	Incidence of symptomatic VTE*		
	< 0.3%	0.3% to 0.5%	> 0.5% to < 1.0%
Maternal pre-pregnancy risk factors			
Age > 35 years	••••[2,4,108,109]		
BMI > 30 kg/m^2 or weight > 90 kg at first antenatal visit	•••••[4,106,108–110]		•[107]
Weight > 120 kg at first antenatal visit		•[110]	
Parity ≥ 2	••••[2,4,106,109]	•[108]	
Smoking >10 cigarettes/day or *current* versus *never* smoked	•••••[2,4,107–109]		
Pre-existing diabetes		•[4]	
Inflammatory bowel disease		•[4]	
Varicose veins	•[4]		
Cancer	•[4]		
Risk factors related to present pregnancy			
Multiple pregnancy	•••[2,4,109]	•[106]	
ART (singleton)		••[3,109]	•[109]
ART (twins)			•[109]
Strict bedrest ≥ 7 days + BMI < 25 kg/m^2 at first antenatal visit	•[186]		•[109]
Preeclampsia/pre-existing hypertension	••[4,109]		
IUGR	•[109]		
Preeclampsia + IUGR	•[109]		
Gestational diabetes	••[3,109]		

*Each dot represents one study; the superscript numerals are references to those studies.

the heparins currently available in Canada, as per the manufacturers' recommendations. However, some women may need a dose adjustment because of their weight, and weight increases as pregnancy progresses.

Women who are known to require antepartum thromboprophylaxis should start LMWH once the decision is made and the patient becomes pregnant. For others, ongoing evaluation of the need for antepartum thromboprophylaxis should be made throughout pregnancy, taking into account the patient's risk factors and preferences and the side-effects associated with LMWH. Antepartum thromboprophylaxis should be continued until the onset of labour, and restarted after delivery (see relevant sections).

Recommendations

29. Individual risk assessment for venous thromboembolism should be performed prior to all pregnancies, once pregnancy is achieved, and repeated throughout pregnancy as new clinical situations arise. The woman's preferences and values should be taken into account when considering the use of antepartum thromboprophylaxis. (III-B)
30. Women at increased risk should be advised of the symptoms and signs of venous thromboembolism. (III-B)
31. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for antepartum thromboprophylaxis. (III-A) Low molecular weight heparin doses should be used as per the manufacturer's recommendation. (III-C)
32. Routine anti-Xa and platelet level monitoring are not recommended when a patient is on a prophylactic dose of thromboprophylaxis. (II-2E)
33. We recommend therapeutic thromboprophylaxis during pregnancy in the following situations:
    a. long-term therapeutic anticoagulation used prior to pregnancy for a persistent indication; (III-B)
    b. personal history of multiple previous venous thromboembolism. (III-B)
34. We recommend intermediate or therapeutic thromboprophylaxis during pregnancy in the following situation:
    a. personal history of a previous venous thromboembolism and a high-risk thrombophilia (antithrombin deficiency, antiphospholipid

syndrome) not previously on anticoagulation. (III-B)

35. We recommend prophylactic dose thromboprophylaxis during pregnancy in the following situations (absolute risk > 1%):
    a. personal history of a previous unprovoked venous thromboembolism; (II-2A)
    b. personal history of a previous venous thromboembolism related to oral contraceptives or pregnancy; (II-2A)
    c. personal history of a previous provoked venous thromboembolism and any low risk thrombophilia; (I-A)
    d. asymptomatic homozygous factor V Leiden; (II-2A)
    e. asymptomatic homozygous prothrombin gene mutation 20210A; (III-B)
    f. asymptomatic combined thrombophilia; (III-B)
    g. asymptomatic antithrombin deficiency; (III-B)
    h. non-obstetrical surgery during pregnancy, with the duration of thromboprophylaxis procedure- and patient-dependent; (III-B)
    i. strict antepartum bedrest for ≥ 7 days in a woman with a body mass index of > 25 kg/m^2 at her first antenatal visit. (II-2B)
36. Antepartum thromboprophylaxis for isolated pregnancy-related risk factors is not recommended. (III-E)
37. Antepartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related risk factors where the overall absolute risk of venous thromboembolism is estimated to be > 1%, especially in women admitted to hospital for bedrest. (II-2B)

ASSISTED REPRODUCTIVE TECHNOLOGY

The risk of VTE in women undergoing ART is estimated to be 0.11% per cycle of in vitro fertilization[111]; however, in the presence of severe OHSS it is as high as 0.78%.[112] Additionally, up to 70% of VTEs in OHSS involve the upper extremity, a much higher incidence than expected.[113,114] VTE associated with ART and OHSS may also present weeks or even months after the resolution of the OHSS.[115] There is currently little to guide clinicians in the use of thromboprophylaxis in women undergoing ART. Extrapolating from the observational data from studies in pregnant women, we believe that in women at high risk for VTE (those identified in Table 4), instituting thromboprophylaxis at the start of ovarian stimulation, and maintaining it for the duration of the ART, would be sensible. If pregnancy is achieved, thromboprophylaxis should be continued in the antepartum period.

For women undergoing IVF with no risk factors for VTE, routine thromboprophylaxis is unnecessary. However, for women who develop severe OHSS, thromboprophylaxis should be considered for at least 8 to 12 weeks after resolution of the OHSS. Ongoing need for thromboprophylaxis would depend on whether pregnancy is achieved in that cycle and on the presence of other antepartum risk factors (such as those in Table 5).

Recommendations

38. Routine thromboprophylaxis is not required for all women undergoing ovulation induction. (III-C)
39. If severe ovarian hyperstimulation syndrome occurs with assisted reproductive technology we recommend thromboprophylaxis with low molecular weight heparin for at least 8 to 12 weeks after resolution of the syndrome. (III-B)
40. Thromboprophylaxis with low molecular weight heparin should be considered for any women at increased risk for venous thromboembolism undergoing assisted reproductive technology at the time of ovarian stimulation. (III-B)
41. Women who develop a venous thromboembolism in association with the use of assisted reproductive technology but who do not conceive in that cycle should be treated with therapeutic anticoagulation for a minimum of 3 months. (II-3A) Those who conceive in that assisted reproductive technology cycle should be treated as per recommendations 12 and 13 for acute venous thromboembolism in pregnancy. (I-A, III-C)

PERIPARTUM ANTICOAGULATION AND NEURAXIAL ANAESTHESIA

Management Before Delivery and Neuraxial Anaesthesia

Current consensus guidelines on the use of neuraxial (epidural, spinal, combined spinal/epidural) analgesia or anaesthesia in patients on anticoagulants largely refer to the management of non-obstetric patients.[10,116,117] Similar recommendations for obstetric patients are extrapolated from recommendations for non-obstetric patients and "weak" evidence (e.g. case reports, case series, pharmacokinetic studies), and do not take into account the physiological changes of pregnancy. These changes generally alter the pharmacokinetics of heparin (both LMWH and UH) in the third trimester such that a "prophylactic dose" in the third trimester may be greater than that used early in pregnancy. The recommendations in this document are taken mainly from those of the ASRA.[10] It is important to note that guidelines from other

Table 6. Recommended timing for neuraxial procedures in relation to anticoagulation dosing in pregnant patients.

	Prophylactic dose	Therapeutic dose
Delay between last dose of anticoagulation and neuraxial anesthesia		
UH	Maximum 10 000 IU/d	> 4 hours after stopping IV infusion, when aPTT is normal.
	No delay unless evidence of abnormal coagulation[10]	When aPTT is normal after stopping subcutaneous UH, may be > 12 hours.
LMWH	10 to 12 hours[10]	> 24 hours[10]
Delay between last dose of anticoagulant and removal of neuraxial catheter		
UH	4 hours	When aPTT is normal
LMWH	Minimum 10 to 12 hours	Minimum 24 hours
Delay between neuraxial anaesthesia and restarting anticoagulant		
UH	1 to 8 hours[120]	1 to 8 hours[120]
LMWH	6 to 8 hours after initiation of neuraxial technique	> 24 hours after initiation of neuraxial technique
	> 24 hours if bleeding during the neuraxial block	
	> 4 hours after removal of the neuraxial catheter[10,120]	> 4 hours after removal of the neuraxial catheter[120]

societies may differ[117] and that the recommendations regarding timing may not apply to all types of LMWH. Early consultation with an anaesthesiologist to assess risks and benefits will inform the patient of her options for intrapartum anaesthesia. Full informed consent must be obtained for neuraxial analgesia and the reasons for deciding whether or not to proceed must be documented.

Whenever possible, women should withhold their thromboprophylaxis at the onset of labour or after their dose on the day prior to a planned induction of labour or Caesarean section. For women on therapeutic anticoagulation, a planned date and mode of delivery is recommended to help simplify their peripartum management.

Switching from thromboprophylactic LMWH to a prophylactic dose of UH at term (37 weeks) may allow for more options with respect to labour analgesia, since neuraxial anaesthesia is contraindicated for at least 10 to 12 hours after LMWH but there is no recommended delay after a maximum dose of 10 000 units of UH per day.[118] Although the ASRA Guidelines suggest no delay following up to 10 000 units of UH per day, many anaesthesiologists prefer to wait a minimum of 4 hours. For women on an intermediate or therapeutic LMWH dose, the risks and benefits of discontinuing subcutaneous LMWH and changing to therapeutic subcutaneous or intravenous UH to allow for neuraxial anaesthesia once the aPTT is normal could be considered. The switch is not necessarily advantageous, however, as at these doses coagulation may be impaired for a duration similar to that with either heparin. Although not required with women on 10 000 units of UH or less, some anaesthesiologists would check an aPTT prior to neuraxial anaesthesia in all women on UH.

Recommendations for the interval delay between the last administered dose of heparin and the insertion or removal of a neuraxial blockade or catheter are shown in Table 6. A recent platelet count should be available in the labour suite or before Caesarean section for women on anticoagulants. In the exceptional situation of a pregnant woman who has had a VTE within the past 2 to 4 weeks, peripartum use of intravenous UH during the latent stage of labour may be necessary. In these women the risk of stopping the heparin should be weighed against the benefit of a neuraxial anaesthesia, based on the anticipated duration of labour and mode of delivery. In this situation, neuraxial anaesthesia could be considered 4 hours after discontinuation of intravenous UH if the platelet count and aPTT are normal.

Although a spinal hematoma is a rare complication (estimated incidence is < 1:150 000 with epidural anaesthesia and < 1:220 000 with spinal anaesthetics in healthy patients[119]), it can result in permanent neurological dysfunction.[10,120] If a spinal hematoma is suspected (new onset or progressive neurological signs, back pain, or bowel/bladder dysfunction), early confirmation by MRI should be done and surgical intervention undertaken, if warranted, to achieve better outcomes.[10,121,122] In women on heparin, the co-existence of any factors that can increase the risk of spinal hematoma (e.g. NSAIDs, LDA in combination with heparin, thrombocytopenia, multiple neuraxial attempts, traumatic tap) should prompt a

re-evaluation of the administration of neuraxial anaesthesia, independent of these guidelines. ASA alone does not appear to increase the risk of neuraxial hematomas. However epidural hematomas have been reported in the non-obstetric literature when patients have received a combination of heparin and ASA, even with an 81 mg dose.[123] Neuraxial anaesthesia must be avoided in women who are fully anticoagulated or when there is evidence of altered coagulation (e.g., petechiae, bruising, altered aPTT without APLS, disseminated intravascular coagulation in patients with HELLP syndrome).

Recommendations

42. Women on prophylactic dose, intermediate dose, or therapeutic anticoagulation should have a discussion about options for analgesia/anaesthesia prior to delivery. (III-B)
43. Switching from thromboprophylactic low molecular weight heparin to a prophylactic dose of unfractionated heparin at term (37 weeks) may be considered to allow for more options with respect to labour analgesia. (III-L)
44. Discontinue prophylactic or intermediate dose low molecular weight heparin or unfractionated heparin upon the onset of spontaneous labour or the day prior to a planned induction of labour or Caesarean section. (II-3B)
45. A recent platelet count should be available on admission in labour or before Caesarean delivery in women who have been, or are, on anticoagulants. (III-B)
46. For women on low molecular weight heparin, neuraxial anaesthesia can be administered as a:
    a. prophylactic dose: a minimum of 10 to 12 hours after the last dose; (III-B)
    b. therapeutic dose: after 24 hours since the last dose. (III-B)
47. For women on unfractionated heparin, neuraxial anaesthesia can be administered as a:
    a. prophylactic dose (maximum 10 000 U/day): after no delay; (III-B)
    b. therapeutic intravenous infusion: at least 4 hours after stopping the infusion and when the activated partial thromboplastin time is normal; (III-B)
    c. therapeutic subcutaneous unfractionated heparin: when the activated partial thromboplastin time is normal. This may be 12 hours or longer after the last injection. (III-B)
48. Neuraxial anaesthesia must be avoided in a woman who is fully anticoagulated or in whom there is evidence of altered coagulation. (II-3A)

Postpartum Management of Anticoagulation After Neuraxial Anaesthesia

After delivery, prophylactic heparin can be initiated or resumed in women who had neuraxial anesthesia once hemostasis is confirmed, there are no signs of neurological complications, and after a minimum of 4 hours following neuraxial catheter removal (see Table 6 for timing intervals). For women on intermediate or therapeutic dose LMWH, the first postpartum dose should be given no sooner than 24 hours postpartum and a minimum of 4 hours following neuraxial catheter removal. Federal Drug Administration recommendations for the timing of the first dose of LMWH following removal of a neuraxial catheter.[124] The neuraxial catheter must be removed before the first LMWH dose.[10] For women requiring ongoing therapeutic heparin our recommendations would be (1) intravenous UH: restart, without a bolus, at a rate of 18 U/kg/hour and monitor aPTT every 6 hours, or (2) subcutaneous LMWH: restart with a low dose (5000 U) at a minimum of 4 hours after removal of the neuraxial catheter and increase to therapeutic dose LMWH after 24 hours. Assessment of the risks and benefits of anticoagulation in these patients should be ongoing within the multidisciplinary team. Intermittent pneumatic compression devices postpartum should be considered for these women at higher risk for venous thrombosis.

Recommendations

49. Removal of a neuraxial catheter left in situ postpartum should only be done 4, 10 to 12, or 24 hours following the administration of prophylactic dose unfractionated heparin (maximum 10 000 U/day), prophylactic low molecular weight heparin (single daily dose), or therapeutic dose low molecular weight heparin, respectively, or in the case of therapeutic unfractionated heparin, when the activated partial thromboplastin time is normal. (II-3B)
50. Prophylactic dose low molecular weight heparin (single daily dose) may be started or restarted 4 hours after neuraxial catheter removal, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)
51. Therapeutic low molecular weight heparin may be started or restarted at least 24 hours after a single injection neuraxial block and a minimum of 4 hours after neuraxial catheter removal, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)
52. Subcutaneous unfractionated heparin may be started or restarted at least 1 hour after a single injection neuraxial block, providing there is full

Table 7. Literature review of incidence of postpartum thromboprophylaxis recommended for single risk factors in isolation

	Incidence of symptomatic VTE*	
	1% to 5%	> 5%
Personal history of previous VTE		
Single	••[89,140]	
Asymptomatic thrombophilia		
FVL homozygosity	••[96,181]	•[183]
APLS	•[140]	
Risk factors related to present pregnancy		
Strict antepartum bedrest ≥ 7 days	•[109]	
Risk factors related to delivery and postpartum period		
> 1 L postpartum hemorrhage + postpartum surgery	•[109]	
Peripartum and/or postpartum infection	•[109]	

Incidence of symptomatic VTE postpartum without prophylaxis is > 1%

*Each dot represents one study; the superscript numerals are references to those studies.

neurological recovery and no evidence of active bleeding or coagulopathy. (III-B)

53. Do not administer antiplatelet agents (acetylsalicylic acid or non-steroidal anti-inflammatory drugs) concomitantly with heparin if a neuraxial catheter is left in situ postpartum. (III-D)
54. Women on therapeutic anticoagulation who have received neuraxial anesthesia should be monitored closely for the development of a spinal hematoma. (III-B)

POSTPARTUM THROMBOPROPHYLAXIS

Postpartum PE is a leading cause of maternal mortality in Canada, with up to 17 maternal deaths each year.[125] The "per day" risk is 15- to 35-fold greater in the 6 weeks following delivery than in non-pregnant age-matched control subjects, with the highest risk being in the first 3 weeks.[3,5–7]

It is generally agreed that universal postpartum thromboprophylaxis is neither cost-effective nor recommended.[126,127] However, an institutional policy on the prevention of postpartum VTE is an Accreditation Canada required organizational practice.[128] In weighing the risks of treatment, specifically heparin (see Table 2), versus the potential for a devastating outcome, it seems reasonable again to use an absolute VTE risk of greater than 1% in considering postpartum thromboprophylaxis (Table 7). It is important to carefully evaluate the need for thromboprophylaxis immediately after every delivery and re-evaluate it over the puerperium as additional risk factors present themselves. Women who have been on antepartum thromboprophylaxis will usually require ongoing heparin postpartum, but the reasons for continuing should be revisited. Ideally, the plan for postpartum thromboprophylaxis will have been reviewed with these women prior to delivery. Many women, however, will require thromboprophylaxis for the first time postpartum. The risk versus benefits should be continually weighed in the decision making process.

Observational studies have demonstrated differing biological and clinical risk factors for antenatal versus postpartum VTE.[3,4,106,129] In the case–control study by Jacobsen et al.,[109] most postpartum risk factors, aside from strict antepartum bedrest for 7 days or more, had minimal impact in isolation (Tables 8 and 9). The strongest associations were seen with combined risks. Table 8 lists the factors of sufficient risk to warrant thromboprophylaxis when 2 are present. Table 9 lists weaker associations, warranting 3 or more to raise the absolute VTE risk postpartum to > 1%. Operative vaginal delivery, prolonged labour, extensive perineal trauma, or prolonged repairs have been flagged as risk factors in other guidelines.[11,13] Evidence to support this is lacking and there are no RCTs assessing thromboprophylaxis following vaginal deliveries.

RCTs of heparin after Caesarean section do exist with 236 women randomized over 4 trials.[130–133] A Cochrane systematic review concluded that there was insufficient evidence of the benefit or harm associated with thromboprophylaxis after Caesarean section due to the small numbers and different comparisons.[134] Overall the risk associated with any Caesarean section is modest.[4,106,109,129] Hence, we recommend against thromboprophylaxis following a Caesarean section in the absence of at least one other risk factor in the case of an emergency, and at least two other risk factors for elective Caesarean sections.

Table 8. Literature review of incidence of postpartum thromboprophylaxis recommended for any two risk factors

	Incidence of symptomatic VTE*		
	< 0.3%	0.3% to 0.5%	> 0.5% to > 1.0%
Maternal pre-pregnancy risk factors			
BMI > 30 kg/m^2 at first antenatal visit	•••[106,107,109]	••[4,140]	
Smoking > 10 cigarettes/day or *current* versus *never* smoked	••••[2,4,107,129]	•[109]	
Maternal cardiac disease			•••[4,106,140]
SLE			••[4,140]
Sickle cell disease			•[140]
Inflammatory bowel disease		•[4]	
Varicose veins		•[4]	
Risk factors related to present pregnancy			
Preeclampsia	•[4]	•••[2,3,109]	
Preterm birth	•[4]	•[129]	
IUGR		•[109]	
Gestational diabetes		•[109]	
Placenta previa		•[3]	
Stillbirth		•[4]	
Risk factors related to delivery and postpartum period			
Emergency Caesarean section		••[3,109]	
Any Caesarean section	••••[4,106,129,140]	•[2]	•[170]
>1 L postpartum haemorrhage or transfusion postpartum	•[4]	•[109]	••[129,140]
Combined risk factors			
Preeclampsia + IUGR			• [109]

Incidence of symptomatic VTE postpartum without prophylaxis < 1% in isolation.

*Each dot represents one study; the superscript numerals are references to those studies.

Table 9. Literature review of incidence of postpartum thromboprophylaxis recommended for three or more risk factors

	Incidence of symptomatic VTE*	
	< 0.2%	0.2% to 0.3%
Maternal pre-pregnancy risk factors		
Cancer	•[4]	
Parity ≥ 2	••[4,109]	•[2]
Age > 35 years	•••••[2,4,5,106,109]	
Risk factors related to present pregnancy		
ART		•[109]
Multiple pregnancy	••••[2,4,109,140]	
Placental abruption		•[3]
PROM	•[109]	
Elective Caesarean section	•[109]	•[3]

Incidence of symptomatic VTE postpartum without prophylaxis < 1% in isolation

*Each dot represents one study; the superscript numerals are references to those studies.

As the puerperium is inherently a higher risk period for VTE than the non-pregnant state, good hydration and mobilization should be encouraged for every woman postpartum.

Recommendations

55. Universal postpartum thromboprophylaxis is not recommended. (III-D)
56. Assess women for increased risk of postpartum venous thromboembolism based on antepartum, intrapartum, and postpartum risk factors after every delivery and repeat as new clinical situations arise. (II-2B)
57. Low molecular weight heparin is the preferred pharmacologic agent over unfractionated heparin for postpartum thromboprophylaxis. (III-A) Low molecular weight heparin doses should be used as per the manufacturer's recommendation. (III-C)
58. Pharmacologic thromboprophylaxis postpartum is recommended in the following situations:

    Any 1 of the following risk factors (each with an absolute venous thromboembolism risk > 1%):
    a. history of any prior venous thromboembolism; (II-2A)
    b. any high-risk thrombophilia: antiphospholipid syndrome, antithrombin deficiency, homozygous factor V Leiden or prothrombin gene mutation 20210A, combined thrombophilia; (II-2B)
    c. strict bed rest prior to delivery for 7 days or more; (II-2B)
    d. peripartum or postpartum blood loss of > 1 litre or blood product replacement, and concurrent postpartum surgery; (II-2B)
    e. peripartum/postpartum infection. (II-2B)
59. Postpartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related risk factors when the overall absolute risk is estimated to be greater than 1% drawn from the following groups:
    a. any 2 of the following risk factors (each with an absolute risk of venous thromboembolism < 1% in isolation):
        i. body mass index ≥ 30 kg/m2 at first antepartum visit; (II-2B)
        ii. smoking > 10 cigarettes/day antepartum; (II-2B)
        iii. preeclampsia; (II-2B)
        iv. intrauterine growth restriction; (II-2B)
        v. placenta previa; (II-2B)
        vi. emergency Caesarean section; (II-2B)
        vii. peripartum or postpartum blood loss of > 1 litre or blood product replacement; (II-2B)
        viii. any low risk thrombophilia: PC or PS deficiency, heterozygous factor V Leiden, or prothrombin gene mutation 20210A; (III-B)
        ix. maternal cardiac disease, SLE, sickle cell disease, inflammatory bowel disease, varicose veins, gestational diabetes; (III-B)
        x. preterm delivery; (III-B)
        xi. stillbirth. (III-B)
    b. any 3 or more of the following risk factors (each with an absolute risk of venous thromboembolism < 1% in isolation):
        i. age > 35 years; (II-2B)
        ii. parity ≥ 2; (II-2B)
        iii. any assisted reproductive technology; (II-2B)
        iv. multiple pregnancy; (II-2B)
        v. placental abruption; (II-2B)
        vi. premature rupture of the membranes; (II-2B)
        vii. elective Caesarean section; (II-2B)
        viii maternal cancer. (III-B)

Mechanical Compression Devices

Mechanical methods of thromboprophylaxis include both graded compression stockings and intermittent pneumatic compression devices. Older evidence suggested that graded compression stockings were beneficial in reducing post-operative VTE, leading to their widespread use.[135] However, their benefit has recently been challenged by two large trials in stroke patients (N = 5632). Thigh-high stockings did not reduce symptomatic VTE or proximal DVT,[136] and knee-high stockings increased the risk of thrombosis.[137] In light of this new evidence we do not advocate the routine use of graded compression stockings in postpartum women to reduce the risk of VTE.

Intermittent pneumatic compression devices have not been studied in pregnancy. Following major gynaecologic surgery associated with a high risk of VTE, they are effective if left on for 5 days or until hospital discharge, but not if removed the day after surgery.[138] In general surgery trials, they are associated with fewer major bleeding episodes than heparin but have a lower VTE risk reduction rate.[9] Most of these RCTs were underpowered to prove efficacy in preventing PE or mortality postoperatively.[139] When pharmacologic treatment is not possible, such as with active bleeding, thrombocytopenia, known heparin allergy or HIT, intermittent pneumatic compression devices are a good alternative. In women at very high risk for VTE postpartum (> 10%), combined mechanical and pharmacologic thromboprophylaxis is recommended.

Recommendation

60. Intermittent or sequential pneumatic compression devices are alternatives in women when heparin

is contraindicated postpartum. When the risk of postpartum venous thromboembolism is high they may be used in combination with low molecular weight heparin or unfractionated heparin. (III-B)

Postpartum Thromboprophylaxis: Duration of Anticoagulation

Up to 60% of postpartum PE occurs in the 4 to 6 weeks after delivery.[3,5,7] The duration of thromboprophylaxis varies with the underlying risk factors. Women with prior VTE have the highest risk and require a minimum of 6 weeks.[89,140] Women with persistent risks that will be present throughout the puerperium (e.g. high risk thrombophilia or prolonged immobility), should also have extended thromboprophylaxis for a full 6 weeks.

There is no evidence to guide the duration of treatment in women having only transient antepartum or intrapartum risks. Given the logistics involved in discharging women on heparin injections, individual institutions and practitioners may vary with respect to the duration of postpartum thromboprophylaxis they choose in these cases. Other guidelines recommend both options: until discharge from hospital fully mobile as a minimum[54,118] or up to 1 to 2 weeks postpartum.[11,15]

Recommendation

61. Women with ongoing and persistent risk factors should receive postpartum thromboprophylaxis for a minimum of 6 weeks postpartum. (II-3B)
62. Women with transient antepartum or intrapartum risk factors should receive postpartum thromboprophylaxis until discharged from hospital or up to 2 weeks postpartum. (III-C)

THROMBOPROPHYLAXIS TO PREVENT ADVERSE PREGNANCY OUTCOMES

Adverse Pregnancy Conditions: Screening

In the 1990s reports of an increase in placenta-mediated pregnancy complications (e.g. recurrent miscarriage, late fetal loss, preeclampsia, placental abruption, and intrauterine growth restriction) in women with thrombophilia appeared in the literature.[141–144] Whereas these early studies suggested a weak association between inherited thrombophilia and placenta-mediated pregnancy complications, subsequent prospective cohort studies suggested no association between most thrombophilia and preeclampsia or SGA infants.[127,145–149] Women with APLS do have an increased risk of recurrent and late pregnancy loss.[127,150] However, there is only a weak association between these complications and FVL and no association with PGM.[149] Hence, universal thrombophilia screening in women experiencing adverse pregnancy outcomes is not indicated.[148] What remains unknown is whether more severe placenta-mediated pregnancy complications (e.g. severe or early-onset preeclampsia, SGA < 3rd percentile, major abruption) are more strongly associated with specific thrombophilia and potentially improved with antenatal thromboprophylaxis.

Recommendations

63. Universal screening for thrombophilias in women experiencing adverse pregnancy outcomes (severe preeclampsia, intrauterine growth restriction, stillbirth) is not indicated. (II-2D)
64. Women with recurrent miscarriage or late pregnancy loss should be screened for antiphospholipid syndrome. (I-B)

LMWH to Prevent Recurrent Adverse Pregnancy Conditions

The benefit of heparin plus LDA in women with APLS and recurrent miscarriage or late fetal loss (variably defined in the different studies) is controversial.[151–154] A meta-analysis looking at 5 trials (N = 334) showed that LMWH plus LDA significantly increased the live birth rate (74.3%) compared to LDA alone (55.8%) with a number needed to treat of 5.6, but with significant heterogeneity.[155] This evidence modestly supports screening women with recurrent miscarriage or late pregnancy loss for APLS and using LMWH alone or with LDA to prevent recurrent miscarriage when APLS is confirmed.

Recent RCTs, however, showed no benefit of LMWH alone or LMWH plus LDA versus no treatment or LDA alone to prevent recurrent miscarriage in women without APLS.[156–161] Although there were no significant complications related to LMWH use in these trials, there were reports of injection site bruising and skin reactions highlighting the fact that heparin is not a benign treatment and should not be prescribed in the absence of evidence to support its use.

Given that placental thrombosis is a part of the common pathophysiology of placenta-mediated pregnancy complications, it is plausible that LDA alone, heparin alone, or the combination of LDA plus LMWH might prevent recurrence of adverse pregnancy outcomes in subsequent pregnancies for women with and without thrombophilia.[162–168] A review of 6 trials (N = 848 women) showed that LMWH, compared to no treatment, reduced the risk of early-onset preeclampsia (RR 0.16, 95% CI 0.07 to 0.36), birth before 37 weeks (RR 0.77, 95% CI 0.62 to 0.96), and SGA infants (RR 0.42, 95% CI 0.29 to 0.59) without any significant effect on perinatal mortality.

There was an overall reduction in a composite outcome of complications (preeclampsia, abruption, SGA infants, or fetal loss after 12 weeks) from 42.9% to 18.7% (RR 0.52, 95% CI 0.32 to 0.86).[169] A 2013 Cochrane review of 9 trials (N = 979) concluded that prophylactic dose heparin (UH or LMWH), compared to no treatment, decreased perinatal mortality (RR 0.40, 95% CI 0.20 to 0.78), preterm delivery < 34 weeks (RR 0.46, 95% CI 0.29 to 0.73) and SGA infants (RR 0.41, 95% CI 0.27-0.61) in women at high risk.[170] Although this data appears promising, given that LMWH is not risk free, it should not be used routinely to reduce the risk of recurrence of all placenta-mediated complications in women, with or without thrombophilia, pending the publication of larger trials or individual patient data meta-analysis. APLS has been considered the exception in many centers, extrapolating from experience with recurrent miscarriage. However, despite the common usage of LMWH and LDA to prevent other adverse pregnancy outcomes in women with APLS, there are no published trials that support this practice.

Recommendations

65. Low-dose acetylsalicylic acid or low-dose acetylsalicylic acid plus low molecular weight heparin is recommended in pregnancy in women with confirmed antiphospholipid syndrome. (I-C)
66. Low-dose acetylsalicylic acid plus low molecular weight heparin is not recommended for women with a history of recurrent miscarriage in the absence of confirmed antiphospholipid syndrome. (I-E)
67. Low molecular weight heparin should not be used routinely to reduce the risk of recurrent placenta-mediated complications in women with or without thrombophilia (excluding antiphospholipid syndrome). (I-C)

FUTURE DIRECTIONS

As we now better understand the appropriate diagnosis of DVT in pregnant women, studies elucidating diagnostic strategies for PE during pregnancy which minimize both fetal and maternal radiation exposure are still required. Even as LMWH replaces UH as the anticoagulant of choice in pregnancy, questions surrounding appropriate dosing regimens or the need for monitoring anti-Xa activity still remain.

As we unequivocally accept that VTE prevention is an important strategy to reduce maternal morbidity and mortality, we also recognize that thromboprophylaxis is not without maternal side-effects or costs. In determining the factors associated with an increased risk of VTE, in isolation or in combination, which supersede the risk of thromboprophylaxis, we extrapolated data mostly from retrospective studies. Data from further large prospective registries could yield more information on the absolute risks associated with various biologic and clinical factors, or combination of factors, which would warrant thromboprophylaxis.

We anticipate data from further prospective studies will become available which will shed light on the effectiveness of LMWH, plus or minus LDA, in preventing recurrent adverse pregnancy outcomes in women with or without inherited thrombophilia.

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