CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **The use of anticoagulant therapy during pregnancy is challenging because of the potential for both fetal and maternal complications. This guideline focuses on the management of VTE and thrombophilia as well as the use of antithrombotic agents during pregnancy.**
Methods: **The methods of this guideline follow the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**
Results: **We recommend low-molecular-weight heparin for the prevention and treatment of VTE in pregnant women instead of unfractionated heparin (Grade 1B). For pregnant women with acute VTE, we suggest that anticoagulants be continued for at least 6 weeks postpartum (for a minimum duration of therapy of 3 months) compared with shorter durations of treatment (Grade 2C). For women who fulfill the laboratory criteria for antiphospholipid antibody (APLA) syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic or intermediate-dose unfractionated heparin or prophylactic low-molecular-weight heparin combined with low-dose aspirin (75-100 mg/d) over no treatment (Grade 1B). For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C). For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).**
Conclusions: **Most recommendations in this guideline are based on observational studies and extrapolation from other populations. There is an urgent need for appropriately designed studies in this population.** ***CHEST 2012; 141(2)(Suppl):e691S–e736S***

Abbreviations: APLA = antiphospholipid antibody; aPPT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NNT = number needed to treat; PE = pulmonary embolism; RR = risk ratio; UFH = unfractionated heparin

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.2.1. For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B).

3.0.1. For women receiving anticoagulation for the treatment of VTE who become pregnant, we recommend LMWH over vitamin K antagonists during the first trimester (Grade 1A)**, in the second and third trimesters** (Grade 1B)**, and during late pregnancy when delivery is imminent** (Grade 1A).

3.0.2. For women requiring long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and substituting LMWH for vitamin K antagonists when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Grade 2C).

Remarks: Women who place little value on avoiding the risks, inconvenience, and costs of LMWH therapy of uncertain duration while awaiting pregnancy and a high value on minimizing the risks of early miscarriage associated with vitamin K antagonist therapy are likely to choose LMWH while attempting pregnancy.

3.0.3. For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) who cannot receive danaparoid (Grade 2C).

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C).

4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A).

4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B).

4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).

4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C).

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breast-feed, we suggest continuing this medication (Grade 2C).

5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B).

5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C).

Remarks: Women who are averse to taking medication for very small benefit and those who consider self-injecting a considerable burden will be disinclined to use LMWH for extended thrombosis prophylaxis. Given that the absolute benefit decreases as time from the hyperstimulation event increases, such women will be very disinclined to continue prophylaxis throughout the entire resultant pregnancy.

6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B).

6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).

Remarks: The reduced bleeding risk with mechanical prophylaxis should be weighed against the inconvenience of elastic stockings and intermittent pneumatic compression.

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6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone (Grade 2C).

6.2.4. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital (Grade 2C).

7.1.1. For pregnant women with acute VTE, we recommend therapy with adjusted-dose subcutaneous LMWH over adjusted-dose UFH (Grade 1B).

7.1.2. For pregnant women with acute VTE, we recommend LMWH over vitamin K antagonist treatment antenatally (Grade 1A).

7.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C).

7.1.4. For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).

8.2.1. For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

8.2.2. For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).

8.2.3. For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

8.2.4. For pregnant women receiving long-term vitamin K antagonists, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum, rather than prophylactic-dose LMWH (Grade 2C).

9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).

9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).

9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).

10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for APLAs (Grade 1B).

10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C).

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical

APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B)**.**

10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C)**.**

11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B)**.**

11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B)**.**

12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A)**:**

(a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous-injection or

(b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or

(c) UFH or LMWH (as above) until the 13th week, with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed.

Remarks: For pregnant women with mechanical heart valves, the decision regarding the choice of anticoagulant regimen is so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that we consider the decision to be completely individualized. Women of childbearing age and pregnant women with mechanical valves, should be counseled about potential maternal and fetal risks associated with various anticoagulant regimens, including continuation of vitamin K antagonists with substitution by LMWH or UFH close to term, substitution of vitamin K antagonists by LMWH or UFH until the 13th week and then close to term, and use of LMWH or UFH throughout pregnancy. Usual long-term anticoagulants should be resumed postpartum when adequate hemostasis is assured.

12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older generation prosthesis in the mitral position or history of thromboembolism), we suggest vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C)**.**

Remarks: Women who place a higher value on avoiding fetal risk than on avoiding maternal complications (eg, catastrophic valve thrombosis) are likely to choose LMWH or UFH over vitamin K antagonists.

12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C)**.**

This article is devoted to the use of antithrombotic therapy in pregnant women. Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE; for the prevention and treatment of systemic embolism in patients with mechanical heart valves; and, in combination with aspirin, for the prevention of recurrent pregnancy loss in women with antiphospholipid antibodies (APLAs).

The use of anticoagulation for prevention of pregnancy complications in women with hereditary thrombophilia is becoming more frequent. Given the absence of proven-effective therapy in women with unexplained recurrent pregnancy loss, there is also growing pressure to intervene with antithrombotic therapy in affected women with no known underlying thrombophilia. The use of anticoagulant therapy during pregnancy is challenging because of the potential for fetal and maternal complications.

1.0 Methods

Table 1 describes both the question definition (ie, population, intervention, comparator, and outcomes) and the eligibility criteria for studies considered in each section of the recommendations that follow. We consider the desirable and undesirable fetal and maternal consequences of antithrombotic therapy in the following populations: (1) breast-feeding women, (2) women using assisted reproductive technology, (3) women undergoing cesarean section, (4) pregnant women with newly diagnosed VTE, (5) pregnant women with prior VTE, (6) pregnant women with asymptomatic thrombophilia, (7) pregnant women with a history of pregnancy complications (including pregnancy loss, preeclampsia, fetal growth restriction, and placental abruption), and (8) pregnant women with mechanical heart valves.

Table 1—*[Section 1.0] Structured Clinical Questions*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
Maternal complications of antithrombotic therapy (section 2.0)	• Adverse maternal outcomes of commonly used antithrombotic agents while pregnant	• Pregnant women	• Unfractionated heparin • Low-molecular-weight heparin • Other relevant agents[a]	• No antithrombotic therapy or • Other antithrombotic therapy	• Maternal bleeding (total major) • Maternal bleeding (major: fatal + intracranial) • Maternal bleeding (major: nonfatal + nonintracranial) • Maternal bleeding (minor) • Maternal heparin-induced thrombocytopenia • Maternal heparin-associated osteoporosis • Maternal skin reaction (allergic)	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Fetal complications of antithrombotic therapy during pregnancy (section 3.0)	• Safety of antithrombotic therapy during pregnancy	• Fetuses and children of women using antithrombotic therapy during pregnancy	• Vitamin K antagonists • Unfractionated heparin • Low-molecular-weight heparin • Other relevant agents[a]	• No antithrombotic therapy exposure or • Other antithrombotic agent	• Fetal hemorrhage • Pregnancy loss • Congenital malformations • Developmental delay • Levels or results of coagulation testing in umbilical cord blood • Birth weight (centile); number small for dates	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Use of antithrombotic therapy in nursing mothers (section 4.0)	• Safety of antithrombotic therapy while breast-feeding	• Breast-fed infants of women receiving antithrombotic therapy	• Vitamin K antagonists • Unfractionated heparin • Low-molecular-weight heparin • Other relevant agents[a]	• No antithrombotic therapy exposure or • Other antithrombotic agent	• Infant hemorrhage • Levels or results of coagulation testing in breast milk • Levels or results of coagulation testing in plasma of breast-fed infants	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of VTE with assisted reproductive technology (section 5.0)	• Risk of VTE in women undergoing assisted reproduction -No additional risk factors -Prior VTE -Thrombophilia[b]	• Women using assisted reproductive technology to become pregnant	• No prophylaxis	• No intervention	• Proportion of pregnancies that are successful • DVT • Pulmonary embolism • Mortality • Major bleeding[c] • Bleeding during oocyte retrieval and embryo transfer	• Control arms of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
	• Choice, duration, and (if appropriate) route/dose of prophylaxis	• Women using assisted reproductive technology to become pregnant	• Low-molecular-weight heparin • Unfractionated heparin • Graduated compression stockings • Other relevant agents[a]	• No prophylaxis or • Other intervention	• DVT • Pulmonary embolism • Mortality • Major bleeding[c] • Bleeding during oocyte retrieval and embryo transfer	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of VTE following cesarean section (section 6.0)	• Risk of VTE following cesarean section in women with -No additional risk factors -Prior VTE -Thrombophilia[b] -Other comorbid conditions	• Pregnant women undergoing cesarean section	• No prophylaxis	• No intervention	• DVT • Pulmonary embolism • Embolism • Mortality • Major bleeding[d] • Epidural hematoma	• Control arms of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
	• Choice, duration, and (if appropriate) route/dose of prophylaxis	• Pregnant women undergoing cesarean section	• Low molecular weight heparin • Unfractionated heparin • Graduated compression stockings • Intermittent pneumatic compression • Combined mechanical and pharmacologic prophylaxis • Other relevant agents[a]	• No prophylaxis or • Other antithrombotic strategy	• DVT • Pulmonary embolism • Mortality • Major bleeding: total[d] • Major bleeding[d] • Epidural hematoma	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies • Decision analysis
Treatment of proven acute VTE during pregnancy (section 7.0)	• Choice, route, and dose of antithrombotic therapy	• Pregnant women with proven acute VTE	• Vitamin K antagonists • Unfractionated heparin • Low-molecular-weight heparin • Other relevant agents[a]	• No treatment or • Other antithrombotic therapy or • Therapy in nonpregnant population with acute VTE	• Symptomatic recurrent DVT or pulmonary embolism • Fatal pulmonary embolism • Major bleeding • Postthrombotic syndrome	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
	• Duration of antithrombotic therapy	• Pregnant women with proven acute VTE	• Throughout pregnancy • Throughout pregnancy and 6 wk postpartum (at least 3 mo) • Throughout pregnancy and 6 wk postpartum (at least 6 mo) • Throughout pregnancy and indefinite postpartum	• Other duration	• Symptomatic recurrent DVT or pulmonary embolism • Fatal pulmonary embolism • Major bleeding	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
	• Role of vena caval filters when antithrombotic therapy is contraindicated	• Pregnant women with proven acute VTE	• Venal caval filter	• No vena caval filter	• Symptomatic recurrent DVT or pulmonary embolism • Fatal pulmonary embolism • Major bleeding • Postthrombotic syndrome	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
	• Management of antithrombotic therapy around delivery	• Pregnant women with proven acute VTE	• Elective delivery[e] with discontinuation of antithrombotic therapy 24 to 48 h prior to delivery • No elective delivery,[e] transition to unfractionated heparin • No elective delivery,[e] transition to prophylactic dose of antithrombotic agent • No elective delivery[e] with discontinuation of antithrombotic therapy as soon as labor commences	•Other intervention	• Symptomatic recurrent DVT or pulmonary embolism • Major bleeding: total[d] • Epidural hematoma • Postthrombotic syndrome	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of recurrent VTE in pregnant women with prior VTE (section 8.0)	• Risk of recurrent VTE in pregnant women with: -A single unprovoked event -A single event that was associated with a transient risk factor (all, estrogen-related [OCP, pregnancy]) -Multiple prior events -Thrombophilia[b]	• Pregnant women with prior VTE	• No prophylaxis	• No intervention	• Symptomatic DVT, pulmonary embolism • Mortality • Major bleeding: total • Postthrombotic syndrome	• Control arms of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
	• Choice and (if appropriate) route and dose of antithrombotic prophylaxis	• Pregnant women with prior VTE	• No antepartum prophylaxis, postpartum only -All relevant agents considered[a] • Antepartum and postpartum prophylaxis -All relevant agents considered[a]	• No prophylaxis	• Symptomatic recurrent DVT or pulmonary embolism • Major bleeding: total • Postthrombotic syndrome	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

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Table 1—*Continued*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
Prevention of pregnancy-related VTE in women with thrombophilia (section 9.0)	• Risk of pregnancy-related VTE in women with thrombophilia[b]	• Pregnant women with thrombophilia[b] and no prior VTE	• No prophylaxis	• No intervention	• Symptomatic DVT, pulmonary embolism • Mortality • Major bleeding	• Control arms of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
	• Choice, duration, and (if appropriate) route/dose of prophylaxis	• Pregnant women with thrombophilia[b] and no prior VTE	• No antepartum prophylaxis, postpartum only -Low-molecular-weight heparin -Unfractionated heparin -Other relevant agents[a] -Graduated compression stockings -Combined mechanical and pharmacologic prophylaxis • Antepartum and postpartum prophylaxis -Similar agents as above	• No prophylaxis or • Other intervention	• Symptomatic DVT, pulmonary embolism • Mortality • Major bleeding	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of pregnancy complications in women with thrombophilia[b] (section 10.0)	• Risk of pregnancy complications in women with thrombophilia[b]	• Pregnant women with thrombophilia[b] and a history of pregnancy complications -Recurrent early pregnancy loss[f] -Late pregnancy loss (single)[g] -Late pregnancy loss (multiple)[h] -Pre-eclampsia -Intrauterine growth restriction -Placental abruption	• No prophylaxis	• No intervention	• Recurrent pregnancy complication (as defined under patient population) • Symptomatic DVT, pulmonary embolism • Mortality • Major bleeding	• Control arm of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
	• Choice and (if appropriate) route and duration of antithrombotic prophylaxis	• Pregnant women with thrombophilia[b] (antiphospholipid antibodies vs congenital thrombophilia vs specific congenital thrombophilia) and a history of pregnancy complications -Recurrent early pregnancy loss[f] -Late pregnancy loss (single)[g] -Late pregnancy loss (multiple)[h] -Preeclampsia -Intrauterine growth restriction -Placental abruption	• Aspirin • Unfractionated heparin (± aspirin) • Low-molecular-weight heparin (± aspirin)	• No prophylaxis or • Other antithrombotic strategy	• Recurrent pregnancy complication (as defined under patient population) • Symptomatic DVT, pulmonary embolism • Mortality • Major bleeding	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of recurrent preeclampsia or recurrent pregnancy loss in women without known thrombophilia[b] (section 11.0)	• Choice and (if appropriate) route and duration of antithrombotic prophylaxis	• Pregnant women with no known thrombophilia[b] and prior preeclampsia • Pregnant women with no known thrombophilia and at least two prior pregnancy losses	• Aspirin • Unfractionated heparin (± aspirin) • Low-molecular-weight heparin (± aspirin)	• No prophylaxis	• Recurrent preeclampsia • Recurrent pregnancy loss	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies
Prevention of thromboembolism in pregnant women with mechanical heart valves (section 12.0)	• Risk of thromboembolism in pregnant women with mechanical heart valves	• Pregnant women with mechanical heart valves	• No antithrombotic therapy	• No intervention	• Maternal thromboembolism • Major bleeding: total • Major bleeding: maternal death • Congenital malformations • Fetal/neonatal hemorrhage • Pregnancy loss	• Control arm of randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
	• Choice and (if appropriate) route and dose of antithrombotic therapy	• Pregnant women with mechanical heart valves	• Vitamin K antagonists throughout pregnancy • Unfractionated heparin throughout pregnancy • Low-molecular-weight throughout pregnancy • Vitamin K antagonists substituted with unfractionated heparin during first trimester (at or before 6 wk) • Vitamin K antagonists substituted with low-molecular-weight heparin during first trimester (at or before 6 wk) • Vitamin K antagonists substituted with unfractionated heparin after 6 wk • Vitamin K antagonists substituted with low molecular weight heparin after 6 wk • Aspirin throughout pregnancy	• No antithrombotic therapy or • Other antithrombotic strategy	• Maternal thromboembolism • Major bleeding maternal death • Congenital malformations • Fetal/neonatal hemorrhage • Pregnancy loss	• Randomized controlled trials • Observational studies -Case series -Cohort studies -Case-control studies

PICO = population, intervention, comparator, outcome.

[a]Other relevant agents included in comparisons were selected based on their relevance for a particular question and may include any or all of the following: unfractionated heparin, low-molecular-weight heparin, fondaparinux, danaparoid, direct thrombin inhibitor, novel oral anticoagulants (eg, apixaban, dabigatran, rivaroxaban), aspirin, and thrombolysis.

[b]Thrombophilia is one or a combination of the following: congenital, including antithrombin deficiency, protein C deficiency, protein S deficiency, activated protein C resistance, factor V Leiden, prothrombin gene mutation, persistently elevated factor VIII levels, or antiphospholipid antibodies, including elevated anticardiolipin antibody titers, nonspecific inhibitor/lupus anticoagulant, and antibodies to β_2-glycoprotein I.

[c]For this question, major bleeding would also include bleeding during oocyte harvest and embryo transfer.

[d]For this question, major bleeding would also include epidural hematoma.

[e]Elective delivery refers to planned delivery/scheduled delivery and may include induction of vaginal delivery or cesarean section.

[f]Preferred as defined by three early losses prior to 12 wk; if not able to extract by this definition, then authors' definition and comment were used.

[g]Preferred as defined by single loss at 12 wk or later; if not able to extract by this definition, then authors' definition and comment were used.

[h]Preferred as defined by two or more losses at 12 wk or later; if not able to extract by this definition, then authors' definition and comment were used.

In addition to considering fetal outcomes (eg, pregnancy loss, congenital malformations) and maternal outcomes (eg, mortality, VTE, major maternal hemorrhage), we also consider burden of treatment as an important outcome for pregnant women taking long-term low-molecular-weight heparin (LMWH) or warfarin. When considered relevant, we report deaths (preferably as disease and treatment-specific mortality). Maternal thromboembolism includes DVT and pulmonary embolism (PE) in sections discussing the treatment and prevention of VTE and systemic embolization and valve thrombosis in sections discussing the management of pregnant women with mechanical heart valves. Major nonfatal maternal hemorrhage is defined as a symptomatic bleeding complication noted during pregnancy or within 6 weeks postpartum that involves bleeding into a critical site (intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, pericardial, intramuscular with compartment syndrome, or placental abruption), causing a fall in hemoglobin level of $\geq$ 20 g/L, and bleeding leading to transfusion of two or more units of whole blood or red cells. This definition is in part based on the definition recommended by the International Society on Thrombosis and Haemostasis.[1] Where major bleeding was not explicitly defined in primary research articles, the authors' definition was accepted. Fetal loss refers to loss at any time after confirmation of a viable intrauterine pregnancy, not including elective termination.

A comprehensive English-language literature search (January 2005-January 2010) was conducted to update our existing literature base. We followed the approach articulated by Grades of Recommendations, Assessment, Development, and Evaluation for formulation of recommendations.[2-4] In making recommendations, we have placed the burden of proof with those who would claim a benefit of treatment. Therefore, when there is uncertain benefit and a probability of important harm associated with therapy, we generally recommend against intervention.

There is a paucity of high-quality studies addressing risk factors for the outcomes discussed in this article as well as for the risks and benefits of antithrombotic therapy during pregnancy. Most recommendations, therefore, are based on low- to moderate-quality evidence and mirror our limited confidence in relative effect estimates from studies of antithrombotic treatment during pregnancy. To obtain baseline risk estimates for pregnancy complications, we summarize available observational studies of pregnant women, including case reports and case series of pregnant women in the absence of studies with a cohort design. We then apply the baseline risk estimates to the relative risk estimates to establish anticipated absolute benefits and harms of intervention. In the absence of direct evidence from randomized trials of reasonable quality, indirect evidence from randomized trials in nonpregnant patients is considered applicable to the present patient population (eg, we extrapolate the effect of thromboprophylaxis with LMWH on the incidence of VTE in patients undergoing general surgery to women undergoing cesarean section).

When describing the various regimens of unfractionated heparin (UFH) and LMWH, we use the following short forms:

- Adjusted-dose UFH: UFH subcutaneously every 12 h in doses adjusted to target a midinterval activated partial thromboplastin time (aPTT) into the therapeutic range
- Prophylactic LMWH: for example, dalteparin 5,000 units subcutaneously every 24 h, tinzaparin 4,500 units subcutaneously every 24 h, nadroparin 2,850 units subcutaneously every 24 h, or enoxaparin 40 mg subcutaneously every 24 h (although at extremes of body weight, modification of dose may be required)
- Intermediate-dose LMWH: for example, dalteparin 5,000 units subcutaneously every 12 h or enoxaparin 40 mg subcutaneously every 12 h
- Adjusted-dose LMWH: weight-adjusted or full-treatment doses of LMWH given once daily or bid (eg, dalteparin 200 units/kg or tinzaparin 175 units/kg once daily or dalteparin 100 units/kg every 12 h or enoxaparin 1 mg/kg every 12 h)

Postpartum anticoagulation refers to vitamin K antagonists for 6 weeks with a target INR of 2.0 to 3.0, with initial UFH or LMWH overlap until the INR is $\geq$ 2.0 or prophylactic- or intermediate-dose LMWH for 6 weeks. The term "clinical vigilance" refers to patient and physician alertness to the signs and symptoms of VTE and awareness of the need for timely and appropriate objective investigation of women with symptoms suspicious of DVT or PE. A family history of VTE refers to DVT or PE in a first-degree relative.

1.1 The Implications of Women's Preferences and Values During Pregnancy

In considering women's choices regarding risks and benefits of antithrombotic therapy in pregnancy, two considerations are of particular importance. First, treatment decisions during pregnancy and breast-feeding have implications not only for the health and life of the mother but also for the health and life of the fetus or child. Second, many women prefer to see pregnancy as a normal part of a healthy woman's life course rather than as a medical condition. On the background of these considerations, many factors, including the frequency and type of medication administration; pain, discomfort, and possible side effects; and the need, frequency, and type of testing associated with a given regimen, will affect women's choices.

The weight given to harmful effects (eg, maternal bleeding events, congenital malformations) and burden of treatment (eg, self-injecting with LMWH for 9 months) compared with beneficial effects (eg, avoiding VTE or pregnancy loss) affects trade-offs between benefits and harms of antithrombotic treatment in pregnancy. A systematic review of patient preferences for antithrombotic treatment did not identify any studies of pregnant women.[5] The findings of this systematic review, and the value and preference rating exercise described in Guyatt et al[4] suggest that one VTE should be viewed as more or less equivalent to one major extracranial bleed. Our clinical experience and preliminary results from a cross-sectional interview study (S. M. Bates, MDCM, personal communication, March 27, 2011) to determine the willingness of women with prior VTE who are either pregnant, actively planning a pregnancy, or who may in the future consider pregnancy to receive LMWH prophylaxis during pregnancy for prevention of recurrent VTE suggest that many, but not all women will choose long-term prophylaxis when confronted with the burden of self-injecting with LMWH over several months. Therefore, in general, we only make weak recommendations for long-term prophylaxis with LMWH.

In addition, the burden of long-term prophylaxis or treatment with LMWH or warfarin throughout pregnancy will have an impact on the choice of antithrombotic therapy. Clinical experience suggests that many, but not all women give higher priority to the impact of any treatment on the health of their unborn baby than to effects on themselves, placing a low value on avoiding the pain, cost, and inconvenience of heparin therapy in order to avoid the small risk of even a minor abnormality in their child. Attempts to balance the burden of long-term prophylaxis against the disutility associated with VTE or major bleeding events are further complicated by the fact that all pregnant women will experience the disutility of long-term prophylaxis, whereas only a minority will avoid VTE with treatment (because the baseline risk of such events generally is low).

Recommendations in this article, therefore, reflect our belief that although average women considering antithrombotic therapy

will also want to avoid medicalizing their pregnancy, they will put an extremely high value on avoiding fetal risk. For women who do not share these values, some of the recommendations in this article may not apply. For most recommendations, optimal decision-making will require that physicians educate patients about their treatment options, including their relative effectiveness, the consequences for both mother and baby, the method of administration and monitoring, the likely side effects, and the uncertainty associated with the estimates of all these effects. Once educated, women can participate in the selection of the treatment regimen that best matches their preferences and values.

2.0 Maternal Complications of Anticoagulant Therapy

Maternal complications of anticoagulant therapy are similar to those seen in nonpregnant patients and include bleeding (for all anticoagulants) as well as heparin-induced thrombocytopenia (HIT), heparin-associated osteoporosis, bruising, local allergic reactions, and pain at injection sites for heparin-related compounds.

2.1 UFH Therapy

During pregnancy, UFH can be used for both prevention and treatment of thromboembolism. Prophylactic UFH is typically administered subcutaneously two to three times per day either in fixed doses or doses adjusted to a target a specific anti-Xa UFH level (prophylactic- or intermediate-dose UFH). When used in therapeutic doses, UFH is administered either intravenously by continuous infusion with dose adjustment to achieve a target therapeutic aPTT or subcutaneously by bid injections in doses sufficient to achieve a therapeutic aPTT 6 h after injection.

During pregnancy, the aPTT response to UFH often is attenuated likely because of increased levels of heparin-binding proteins, factor VIII, and fibrinogen.[6] Consequently, the use of an aPTT range that corresponds to therapeutic heparin levels in nonpregnant patients might result in higher dosing (and heparin levels) in pregnant women than in nonpregnant patients. However, it is not clear whether this translates into excessive bleeding because the reported rates of bleeding using the standard aPTT range appear to be low. In a retrospective cohort study of 100 pregnancies in 77 women,[7] the rate of major antepartum bleeding in pregnant women treated with UFH was 1% (95% CI, 0.2%-5.4%), which is consistent with reported rates of bleeding associated with heparin therapy in nonpregnant patients[8] and with warfarin therapy[9,10] when used for the treatment of DVT.

Therapeutic doses of subcutaneous UFH can cause a persistent anticoagulant effect, which can complicate its use prior to delivery. In a small cohort study, prolongation of the aPTT persisted for up to 28 h after the last injection of adjusted-dose subcutaneous heparin.[11] The mechanism for this prolonged effect is unclear. A similar effect has not been noted with IV UFH.

Thrombocytopenia during pregnancy is not uncommon, and pregnancy-specific causes[12] should be differentiated from IgG-mediated thrombocytopenia or HIT, which occurs in ~3% of nonpregnant patients receiving UFH.[13] The diagnosis, prevention, and treatment of HIT are described in Linkins et al[14] in these guidelines. In pregnant women who develop HIT and require ongoing anticoagulant therapy, use of the heparinoid danaparoid sodium is recommended because it is an effective antithrombotic agent[15] that does not cross the placenta[16-18] and has low cross-reactivity with UFH[19]; therefore, it rarely produces HIT (danaparoid was withdrawn from the US market in 2002). Although there are reports of fondaparinux[20,21] being used for this indication in pregnancy, experience with this agent during pregnancy is too limited to recommend fondaparinux over danaparoid.

Long-term treatment with UFH has been reported to cause osteoporosis in both laboratory animals and humans.[22-30] A number of studies have attempted to quantify the risk of osteoporosis during prolonged treatment (> 1 month) with UFH. Symptomatic vertebral fractures have been reported to occur in ~2% to 3% of the patient population, and significant reductions of bone density have been reported in up to 30%.[22,23] A small study (n = 40) reported an even higher percentage of fractures (15%) when older nonpregnant patients were treated with bid subcutaneous injections of 10,000 units UFH for a period of 3 to 6 months.[26]

Adverse skin reactions to UFH include bruising, urticarial rashes, erythematous well-circumscribed lesions (because of a delayed type 4 hypersensitivity reaction), skin necrosis (often due to vasculitis), and HIT. The true incidence of skin reactions caused by UFH is unknown.[31]

2.2 LMWH Therapy

Despite a paucity of supportive data from controlled trials or even large prospective observational studies, LMWH is now commonly used for prophylaxis and treatment of maternal thromboembolism. This change in practice is based largely on the results of large trials in nonpregnant patients, showing that LMWHs are at least as safe and effective as UFH for the treatment of VTE[32,33] and acute coronary syndromes[34] as well as for prophylaxis in high-risk patients.[35]

Retrospective analyses and systematic reviews suggest that the incidence of bleeding in pregnant

women receiving LMWH is low.[36-38] A systematic review of 64 studies that included 2,777 pregnancies in which LMWH was used reported that the frequencies of significant bleeding were 0.43% (95% CI, 0.22%-0.75%) for antepartum hemorrhage, 0.94% (95% CI, 0.61%-1.37%) for postpartum hemorrhage, and 0.61% (95% CI, 0.36%-0.98%) for wound hematoma, giving an overall frequency of 1.98% (95% CI, 1.50%-2.57%).[38] The risk of HIT appears much lower with LMWH than with UFH.[13,37,38]

Evidence suggests that LMWHs carry a lower risk of osteoporosis than UFH. In a study by Monreal and colleagues[26] in which 80 patients (men and women; mean age, 68 years) with DVT were randomized to either subcutaneous dalteparin 5,000 units bid (intermediate dose) or subcutaneous UFH 10,000 units bid for a period of 3 to 6 months, the risk of vertebral fractures with UFH (six of 40 [15%] patients; 95% CI, 6%-30%) was higher than with dalteparin (one of 40 [3%] patients; 95% CI, 0%-11%). In another randomized trial of 44 pregnant women allocated to prophylactic doses of dalteparin (n = 21) or UFH (n = 23),[27] bone density did not differ between women receiving dalteparin and those in a concurrent nonrandomized cohort of healthy pregnant women but was significantly lower in those receiving UFH. A prospective observational study in which 55 pregnant women treated with prophylactic LMWH and aspirin and 20 pregnant untreated volunteers reported similar results.[39] Finally, in an a priori substudy of an ongoing randomized comparison of prophylactic LMWH (subcutaneous dalteparin 5,000 units/d) with placebo for prevention of pregnancy complications, there was no difference between the two groups with respect to mean bone mineral density.[40]

Despite these reassuring data, there have been case reports[41-44] of symptomatic osteoporosis occurring with LMWH. Osteoporosis may be due to individual susceptibility, reflecting the presence of risk factors for osteoporosis, a variable effect of different LMWH preparations or doses on bone density, or a combination of both. Risk factors that make women susceptible to this complication when exposed to LMWH in pregnancy remain to be identified.

Adverse skin reactions similar to those seen with UFH can also occur with LMWH, although the frequency appears reduced in patients receiving the latter. The reported incidence ranges from 1.8% to 29%.[38,45] Most LMWH-induced skin lesions are benign; however, HIT should be excluded.[46]

Recommendation

2.2.1. For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B)**.**

3.0 Fetal Complications of Antithrombotic Therapy During Pregnancy

3.1 Vitamin K Antagonist Exposure In Utero

Vitamin K antagonists cross the placenta and have the potential to cause fetal wastage, bleeding in the fetus, and teratogenicity.[47-58] In a systematic review of the literature published between 1966 and 1997 that examined fetal and maternal outcomes of pregnant women with prosthetic valves, Chan and colleagues[49] provided pooled estimates of risks associated with the following approaches: (1) use of vitamin K antagonists throughout pregnancy, (2) replacement of vitamin K antagonists with UFH from 6 to 12 weeks, and (3) UFH use throughout pregnancy (Tables S1, S2) (tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement; see the "Acknowledgments" for more information). The authors found that the use of vitamin K antagonists throughout pregnancy was associated with congenital anomalies in 35 of 549 live births (6.4%; 95% CI, 4.6%-8.9%). A subsequent systematic review covering the years 2000 to 2009 (Tables S1, S2) reported a slightly lower risk estimate (21/559 [3.7%]; 95% CI, 1.9%-4.8%).[50]

In both reviews, the most common fetal anomaly was coumarin or warfarin embryopathy consisting of midfacial hypoplasia and stippled epiphyses. Limb hypoplasia has been reported in up to one-third of cases of embryopathy.[51] Embryopathy typically occurs after in utero exposure to vitamin K antagonists during the first trimester of pregnancy.[48] The results of a recently published multicenter European study not included in the systematic reviews, in which the pregnancies of 666 consenting women who contacted one of 12 Teratology Information Services between 1988 and 2004 seeking advice about gestational exposure to vitamin K antagonists were prospectively followed, also suggests that the risk of coumarin embryopathy is not high.[58] Although the frequency of major birth defects after any first trimester exposure to vitamin K antagonists was increased compared with that seen in a control group of 1,094 women counseled during pregnancy about exposures known to be nonteratogenic (4.8% vs 1.4%, respectively; OR, 3.86; 95% CI, 1.86-8.00), there were only two cases of embryopathy among 356 live births (0.6%). Both cases involved exposure to phenprocoumon until at least the end of the first trimester.

The substitution of heparin at or prior to 6 weeks appears to eliminate the risk of embryopathy, raising the possibility that vitamin K antagonists are safe with regard to embryopathy during the first 6 weeks of gestation. In the systematic review by Chan and colleagues,[49] none of the 125 live births (95% CI,

0%-3.0%) in which vitamin K antagonists were replaced with UFH at or before 6 weeks gestation or UFH used throughout pregnancy was associated with congenital fetal anomalies. In the European multicenter Teratology Information Services study, there were no cases of embryopathy among 235 live births when vitamin K antagonists were discontinued before week 8 after the first day of the last menstrual period.[58]

Vitamin K antagonists have also been associated with CNS abnormalities after exposure during any trimester.[48] Two patterns of CNS damage have been described: dorsal midline dysplasia (agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy) and ventral-midline dysplasia leading to optic atrophy.[48] These complications are uncommon.[48,49]

Although one cohort study reported that the use of coumarins during the second and third trimester was not associated with major risks for abnormalities in growth and long-term development of offspring, the authors noted an increased risk of minor neurodevelopmental problems (OR, 1.7; 95% CI, 1.0-3.0) in children exposed to coumarins in the second and third trimester of pregnancy compared with age-matched nonexposed children (14% vs 8%, respectively).[59] However, these minor neurodevelopmental problems are likely of minor importance because there were no differences in mean IQ or performance on tests for reading, spelling, and arithmetic between exposed and nonexposed children.[60]

Vitamin K antagonists have been linked to an increased risk of pregnancy loss[49,50,58,61] and can cause fetal hemorrhagic complications likely because the fetal liver is immature and fetal levels of vitamin K-dependent coagulation factors are low. Fetal coagulopathy is of particular concern at the time of delivery when the combination of the anticoagulant effect and trauma of delivery can lead to bleeding in the neonate. The risk of delivering an anticoagulated infant can be reduced by substituting UFH or LMWH for vitamin K antagonists approximately 3 weeks prior to planned delivery[61] and discontinuing these medications shortly before delivery. Others have advocated the use of planned cesarean section at 38 weeks with only a brief (2 to 3 day) interruption of anticoagulant therapy.[62] This approach resulted in good neonatal and maternal outcomes in a study of 30 babies. Cesarean section is not without risk and is not recommended for other conditions associated with an increased risk of neonatal intracranial hemorrhage at the time of delivery (eg, immune thrombocytopenia purpura).

3.1.1 Thromboprophylaxis in Women Using Vitamin K Antagonists and Planning Pregnancy: Physicians should counsel women receiving vitamin K antagonist therapy and contemplating pregnancy about the risks of vitamin K antagonist therapy before pregnancy occurs. If pregnancy is still desired, the following two options can reduce the risk of warfarin embryopathy:

1. Performance of frequent pregnancy tests and substitution of adjusted-dose LMWH or UFH for warfarin when pregnancy is achieved or
2. Replacement of vitamin K antagonists with LMWH or UFH before conception is attempted

Both approaches have limitations. The first assumes that vitamin K antagonists are safe during the first 4 to 6 weeks of gestation. Although the second approach minimizes the risks of early miscarriage associated with vitamin K antagonist therapy, it lengthens the duration of exposure to heparin and, therefore, is costly and exposes the patient to a greater burden of treatment associated with the use of parenteral anticoagulants.

3.2 UFH Exposure In Utero

UFH does not cross the placenta[63] and, therefore, does not have the potential to cause fetal bleeding or teratogenicity; although bleeding at the uteroplacental junction is possible. Several studies provide high-quality evidence that UFH therapy is safe for the fetus.[7,47,64]

3.3 LMWH Exposure In Utero

As determined by measurement of anti-Xa activity in fetal blood, LMWH also does not cross the placenta.[65,66] There is no evidence that LMWH causes teratogenicity or increases the risk of fetal bleeding.[36]

3.4 Danaparoid Exposure In Utero

Animal experiments and human case reports suggest negligible transport of danaparoid across the placenta[16-18,67] Thus, there is no demonstrable fetal toxicity with maternal danaparoid use. However, the quality of evidence available to support that claim is low. (Note: Danaparoid was withdrawn from the US market in 2002.)

3.5 Pentasaccharide Exposure In Utero

Although no placental passage of fondaparinux was demonstrated in a human cotyledon (small lobe on the uterine or maternal surface of the placenta) model,[68] anti-Xa activity (at approximately one-tenth the concentration of maternal plasma) was found in the umbilical cord plasma of five newborns of mothers treated with fondaparinux.[69] Although there have been a small number of reports of the successful use of this agent in pregnant woman,[70-76] most of these involve second trimester or later exposure. Thus, the quality of evidence regarding supporting use of fondaparinux in pregnancy is very low. Potential deleterious effects on the fetus cannot be excluded.

3.6 Parenteral Direct Thrombin Inhibitor Exposure In Utero

Investigations have documented placental transfer of r-hirudin in rabbits and rats.[77,78] Although small numbers of case reports have documented successful outcomes with r-hirudin use in pregnancy,[77,79,80] there are insufficient data to evaluate its safety. Three case reports have been published describing the use of argatroban late in pregnancy.[81-83] There are no published reports on the use of bivalirudin.

3.7 New Oral Direct Thrombin and Anti-Xa Inhibitor Exposure In Utero

Pregnant women were excluded from participating in clinical trials evaluating these new agents. There are no published reports describing the use of new oral direct thrombin inhibitors (eg, dabigatran) or anti-Xa inhibitors (rivaroxaban, apixaban) in pregnancy. The Summaries of Product Characteristics for dabigatran and rivaroxaban describe animal reproductive toxicity.[84,85] The human reproductive risks of these medications are unknown.

3.8 Aspirin Exposure In Utero

Aspirin crosses the placenta, and animal studies have shown that aspirin may increase the risk of congenital anomalies. Several systematic reviews have examined the safety of aspirin use during pregnancy (Tables S1-S3).[86-88] A meta-analysis of 31 randomized studies comparing antiplatelet agents with either placebo or no antiplatelet agents in 32,217 pregnant women at risk for developing preeclampsia[86] reported that aspirin therapy was not associated with an increase in the risk of pregnancy loss, neonatal hemorrhage, or growth restriction. However, in a meta-analysis of eight studies that evaluated the risk of congenital anomalies with aspirin exposure during the first trimester, aspirin use was associated with a twofold increase in the risk for gastroschisis (OR, 2.37; 95% CI, 1.44-3.88).[87] The validity of this risk estimate is questionable because of a significant risk of bias in the contributing studies.

One population-based study did note an increased risk of miscarriage with aspirin use that was greatest when aspirin was taken around the time of conception[89]; however, the number of aspirin users was small, aspirin doses were unknown, and users may have had conditions associated with an increased risk of pregnancy loss.[90] A meta-analysis of seven randomized trials in which women started aspirin later in pregnancy (Tables S1, S3) failed to establish or refute an increase in risk of miscarriage with aspirin compared with placebo (risk ratio [RR], 0.92; 95% CI, 0.71-1.19 for first or second trimester exposure; RR, 1.3; 95% CI, 0.63-2.69 for first trimester exposure only).[88]

3.9 Thrombolysis During Pregnancy

Although investigations with ^{131}I-labeled streptokinase or tissue plasminogen activator showed minimal transplacental passage,[91] concerns remain about the use of thrombolytic therapy during pregnancy due to maternal and placental effects. Although there have been reports of successful thrombolysis in pregnancy (most involving streptokinase),[91-94] the number of cases is small. Given this and limitations of available data regarding the safety of this intervention in pregnancy, the use of thrombolytic therapy is best reserved for life-threatening maternal thromboembolism.[95]

Recommendations

3.0.1. For women receiving anticoagulation for the treatment of VTE who become pregnant, we recommend that LMWH over vitamin K antagonists during the first trimester (Grade 1A)**, in the second and third trimesters** (Grade 1B)**, and during late pregnancy when delivery is imminent** (Grade 1A)**.**

3.0.2. For women requiring long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and substituting LMWH for vitamin K antagonists when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Grade 2C)**.**

Remarks: Women who place little value on avoiding the risks, inconvenience, and costs of LMWH therapy of uncertain duration while awaiting pregnancy and a high value on minimizing the risks of early miscarriage associated with vitamin K antagonist therapy will probably choose LMWH while attempting pregnancy.

3.0.3. For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (including HIT) who cannot receive danaparoid (Grade 2C)**.**

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C)**.**

4.0 Use of Anticoagulants in Breast-feeding Women

In order for a drug to pose a risk to the breast-fed infant, not only must it be transferred and excreted into breast milk but also it must be absorbed from

the infant's gut. Drugs that are poorly absorbed are unlikely to affect the neonate. Lipid-soluble drugs with a low molecular weight that are not highly protein bound are more likely to be transferred into breast milk.[96]

4.1 Use of Vitamin K Antagonists in Breast-feeding Women

Despite a lack of data suggesting any harmful effect to breast-feeding infants, many obstetricians remain reluctant to prescribe warfarin to lactating women. This might reflect concerns that less polar, more lipophilic vitamin K antagonists rarely used in North America (eg, phenindione, anisindione, and phenprocoumon) might be excreted into breast milk.[97] Warfarin, the oral anticoagulant prescribed for most patients in North America, is polar, nonlipophilic, and highly protein bound. There have been two convincing reports demonstrating that warfarin is not detected in breast milk and does not induce an anticoagulant effect in the breast-fed infant when nursing mothers consume the drug.[98,99] Acenocoumarol, which is commonly used in Europe, has similar properties (Tables S4, S5).[100,101] Therefore, the use of warfarin and acenocoumarol in women who require postpartum anticoagulant therapy is safe.

4.2 Use of UFH and LMWH in Breast-feeding Women

Because of its high molecular weight and strong negative charge, UFH does not pass into breast milk and can be safely given to nursing mothers.[102] In a case series of 15 women receiving 2,500 International Units of LMWH after cesarean section, there was evidence of excretion of small amounts of LMWH into the breast milk in 11 patients (Tables S4, S5).[103] However, given the very low bioavailability of oral heparin, there is unlikely to be any clinically relevant effect on the nursing infant.

4.3 Use of Danaparoid in Breast-feeding Women

Very little is known about the passage of danaparoid into breast milk. A small number of case reports have reported no or very low anti-Xa activity in the breast milk of danaparoid-treated women.[77] Because danaparoid is not absorbed by the GI tract after oral intake, it is unlikely that any anticoagulant effect would appear in breast-fed infants.

4.4 Use of Fondaparinux in Breast-feeding Women

According to the manufacturer's prescribing information, fondaparinux was found to be excreted in the milk of lactating rats.[104] There are no published data on the excretion of fondaparinux into human milk, and the effects on the nursing infant are unknown. As a negatively charged oligosaccharide, only minor amounts of fondaparinux are expected to pass the intestinal epithelial barrier after oral administration, and significant absorption by the nursing infant is unlikely.[105] However, the manufacturer recommends that caution be used when administering fondaparinux to breast-feeding women.

4.5 Use of Parenteral Direct Thrombin Inhibitors in Breast-feeding Women

In a single-case report, no r-hirudin was detected in the breast milk of a nursing mother with a therapeutic plasma hirudin level.[106] Enteral absorption of r-hirudin appears to be low.[78] Therefore, it is unlikely that exposed infants would experience a significant anticoagulant effect, even if small amounts of r-hirudin appear in breast milk.

4.6 Use of New Oral Direct Thrombin and Factor Xa Inhibitors in Breast-feeding Women

Breast-feeding women were excluded from trials evaluating new oral direct thrombin and anti-Xa inhibitors, and there are no clinical data on the effect of these agents on breast-fed infants. The Summary of Product Characteristics for rivaroxaban notes that animal data indicate that this agent is secreted into breast milk.[85] The manufacturers of dabigatran and rivaroxaban both recommend against using these medications in breast-feeding women.[84,85]

4.7 Use of Aspirin in Breast-feeding Women

Although aspirin is a polar, acidic drug that is poorly lipid soluble and highly bound to plasma proteins, maternal aspirin ingestion is associated with excretion of salicylates into breast milk.[107] There are, therefore, potential risks of platelet dysfunction and GI bleeding in nursing infants of mothers using high doses of this drug.[107,108] Metabolic acidosis has been reported in breast-fed infants of mothers taking several grams of aspirin per day.[109,110] Theoretically, nursing infants of mothers taking aspirin could be at risk for developing Reye syndrome.[107] The use of low-dose aspirin (< 100 mg/d) late in pregnancy was not associated with significant effects on neonatal platelet function.[111,112] In a prospective study of 15 breast-feeding mothers taking aspirin therapy, no negative effects were noted (Tables S4, S5).[113]

Recommendations

4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A)**.**

4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B).

4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).

4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin and factor Xa inhibitors (Grade 1C).

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breast-feed, we suggest continuing this medication (Grade 2C).

5.0 VTE in Patients Using Assisted Reproductive Technology

Assisted reproductive technology, which refers to all treatments or procedures involving in vitro handling of human oocytes and sperm or embryos for the purpose of achieving pregnancy,[114,115] may be associated with VTE. Data regarding the frequency of VTE, however, comprise predominantly of case reports, case series, and relatively small cohort studies (Table S6).[116-121] In two large retrospective series of patients undergoing in vitro fertilization, thrombosis complicated 0.1% (95% CI, 0%-0.3%)[116] and 0.3% (95% CI, 0%-0.8%)[117] of cycles. A hospital-based case-control study demonstrated a fourfold increase in antenatal VTE with assisted reproductive technology for singleton pregnancies and a sixfold incidence in twin pregnancies but no statistically significant association with postpartum VTE.[121] Thus, although in vitro fertilization appears to be a risk factor for antepartum thromboembolism, the overall absolute incidence of symptomatic thrombosis appears to be low.

The risk of thrombosis may be higher in women with ovarian hyperstimulation syndrome, with an incidence of thrombosis of up to 4.1% (95% CI, 1.1%-13.7%) in severe cases.[116] In a review of thrombosis associated with assisted reproductive technology, Chan and colleagues[122] identified 61 reports of venous thrombosis (49 cases involving the veins of the neck and arm) and 35 arterial events. Ovarian hyperstimulation syndrome was reported in 90% of arterial cases and 78% of venous events. In 98% of cases, thrombosis occurred after ovulation induction. Venous events were delayed compared with those involving the arterial circulation (42.4 days after embryo transfer and 10.7 days post-transfer, respectively).[122]

5.1 Prevention of VTE in Patients Undergoing Assisted Reproductive Technology

The bleeding risk most relevant to this population is intraabdominal and vaginal bleeding. The estimates of normal blood loss during uncomplicated oocyte retrieval vary, ranging from approximately 230 mL in one prospective cohort of 220 women[123] to 13 mL (range, 0-98 mL) in a study of 83 women.[124] Although patient-important vaginal bleeding appears to occur in up to 2% to 3% of patients, significant intraabdominal bleeding is much less common ($\leq$ 0.5% procedures) (Table S7).[120,125-132] Whether these risks are increased with antithrombotic prophylaxis is uncertain.

All studies that address the impact of prophylaxis in in vitro fertilization have important limitations, and the number of patients who have received anticoagulants is too small to draw any conclusions about safety and efficacy (Table S8).[133-135] Therefore, we used indirect evidence from a meta-analysis of thromboprophylaxis in patients undergoing hip arthroplasty[136] to estimate the relative effects LMWH prophylaxis in assisted reproductive technology. Table 2 and Table S9 summarize the quality of evidence and anticipated absolute effects of thrombosis prophylaxis in women with and without ovarian hyperstimulation syndrome. We rate the quality of evidence as low due to indirectness of the population and intervention and due to considerable imprecision in risk estimates for major bleeding events and VTE. In women with severe ovarian hyperstimulation syndrome, thromboprophylaxis may result in 26 fewer VTE per 1,000 women treated (number needed to treat [NNT] of 39 [given an estimated baseline risk of VTE of 4%]), with no increased risk of significant bleeding. However, in women without ovarian hyperstimulation syndrome in whom the baseline risk of VTE is estimated to be $\sim$0.2%, the use of LMWH prophylaxis is of very limited value (NNT, 781).

Data regarding the risk of VTE in women with thrombophilia or prior VTE who undergo assisted reproduction are lacking. Given the low baseline risk of VTE associated with assisted reproduction, if the magnitude of relative risk increases is similar to that reported with pregnancy-related VTE (sections 8 and 9), women with low-risk thrombophilias or prior VTE associated with major transient risk factors will receive only very small benefit from prophylaxis.

Dosage and duration of thromboprophylaxis after assisted reproductive therapy has not been well studied. If LMWH is used in women who develop ovarian hyperstimulation, extension of prophylaxis for 4 to 8 weeks postresolution of hyperstimulation[114] or throughout any resultant pregnancy and into the postpartum period[115] has been suggested given that

Table 2—*[Section 5.1.1, 5.1.2] Summary of Findings: Prophylactic-Dose LMWH vs No Thromboprophylaxis for Women Who Undergo Assisted Reproductive Therapy*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects During Pregnancy	
				Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE, DVT, and pulmonary embolism	1,953 (6 RCTs), 27-35 d postoperative	Low due to indirectness[b] and imprecision[a]	RR 0.36 (0.20-0.67)	Without severe ovarian hyperstimulation syndrome	
				2 VTE per 1,000[c]	1 fewer VTE per 1,000 (from 2 fewer to 0 fewer)
				With severe ovarian hyperstimulation syndrome	
				40 VTE per 1,000[c]	26 fewer per 1,000 (from 32 fewer to 13 fewer)
Major bleed	5,456 (7 RCTs), 3 wks-9 mo	Low due to indirectness[b] and imprecision[a]	RR 0.43 (0.11-1.65)	30 bleeding events per 1,000[c]	No significant difference 17 fewer bleeding events per 1,000 (from 27 fewer to 20 more)

GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; RR = risk ratio.

[a]Rated down for imprecision due to imprecise control group risk estimates for bleeding events and for VTE in the subset of women with ovarian hyperstimulation (Tables S6-S8).

[b]The population did not include pregnant women. Different doses of LMWH were used, treatment was initiated variably before or after surgery with a duration of ~7 d (in hospital). Outcomes were variably reported; meta-analysis also provides other outcomes such as mortality, asymptomatic DVT, and specific bleed outcomes (wound hematoma, transfusion). Follow-up varied between trials from 3 wk to 9 mo.

[c]Control group risk for VTE and major bleed come from observational studies of women undergoing assisted reproductive technology, with many studies following women until delivery (Tables S6-S8).

most reported events have developed days to weeks (range, 2 days-11 weeks) after resolution of ovarian hyperstimulation.[115] However, given the lack of a clear association between assisted reproductive technology and postpartum events,[117,121] continuing anticoagulant prophylaxis after delivery is less likely to be of benefit.

Recommendations

5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B)**.**

5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C)**.**

Remarks: Women who are averse to taking medication for very small benefit and those who consider self-injecting a considerable burden will be disinclined to use LMWH for extended thrombosis prophylaxis. Given that the absolute benefit decreases as time from the hyperstimulation event increases, such women will be very disinclined to continue prophylaxis throughout the entire resultant pregnancy.

6.0 VTE Following Cesarean Section

6.1 Risk of VTE Following Cesarean Section

The puerperium is the time of maximal daily risk of pregnancy-associated VTE.[137,138] Several observational studies have assessed the risk of VTE after cesarean section, with absolute risk estimates ranging from < 1 in 1,000 up to 18 of 1,000 cesarean deliveries.[121,139-148] However, studies based on hospital records and disease coding may result in an underestimation of the true incidence of symptomatic VTE.[149] A Norwegian study of 59 low-risk women undergoing elective cesarean section who underwent screening for DVT using triplex ultrasonography (compression ultrasonography, color Doppler echocardiography, and spectral Doppler echocardiography) 2 to 5 days after delivery and followed up for 6 weeks reported that none had symptomatic or asymptomatic VTE (95% CI, 0%-6.1%).[144] A small prospective study in which patients after cesarean section underwent screening ultrasounds at hospital discharge and 2 weeks postpartum and were followed for 3 months reported a symptomatic event rate of five of 1,000 (95% CI, 0.1%-2.8%).[147] This is consistent with estimates based on hospital discharge data antedating the use of thromboprophylaxis.[138,140]

Observational studies provide evidence concerning risk factors for VTE in pregnant women (Tables S10, S11)[121,146,148,150-152]; these are likely to be relevant in women undergoing cesarean section. In assessing risk in this setting, the number of risk factors, the magnitude of risk associated with these factors, and their impact when occurring together are all relevant. Table 3 provides an overview of major and minor risk factors we suggest clinicians use to identify women at increased risk of VTE after cesarean section. The presence of one major or at least two minor risk factors will indicate whether patients qualify for

Table 3—*[Section 6.2.1-6.2.4] Risk Factors for VTE Resulting in a Baseline Risk of Postpartum VTE of > 3%*

Major risk factors (OR > 6): presence of at least one risk factor suggests a risk of postpartum VTE > 3%
Immobility (strict bed rest for ≥ 1 week in the antepartum period)
Postpartum hemorrhage ≥ 1,000 ml with surgery
Previous VTE
Preeclampsia with fetal growth restriction
Thrombophilia
Antithrombin deficiency[a]
Factor V Leiden (homozygous or heterozygous)
Prothrombin G20210A (homozygous or heterozygous)
Medical conditions
Systemic lupus erythematosus
Heart disease
Sickle cell disease
Blood transfusion
Postpartum infection
Minor risk factors (OR > 6 when combined): presence of at least two risk factors or one risk factor in the setting of emergency cesarean section suggests a risk of postpartum VTE of > 3%
BMI > 30 kg/m^2
Multiple pregnancy
Postpartum hemorrhage > 1 L
Smoking > 10 cigarettes/d
Fetal growth restriction (gestational age + sex-adjusted birth weight < 25th percentile)
Thrombophilia
Protein C deficiency
Protein S deficiency
Preeclampsia

Data from Jacobsen et al,[121] Jacobsen et al,[144] Lindqvist et al,[146] Simpson et al,[148] Knight,[150] Robertson et al,[151] and James et al.[152]

[a]Although the OR in a systematic review was 4.69, CIs were wide and numbers small. Further, other retrospective studies have calculated ORs of 282 (95% CI, 31-2,532) for type 1 antithrombin deficiency and 28 (95% CI, 5.5-142) for type 2 deficiency.[153] Thus, antithrombin deficiency has been left as a major risk factor.

our weak recommendation for thrombosis prophylaxis (section 6.2). Extrapolating from high-risk populations,[154-156] the combination of LMWH prophylaxis with mechanical methods may be of benefit when multiple major risk factors for VTE are present. Further, when major risk factors continue in the puerperium, consideration should be given to extending prophylaxis for the 6 weeks during which pregnancy-associated prothrombotic changes may persist.[137]

6.2 Thromboprophylaxis Following Cesarean Section

A recent systematic review[157] identified four studies (830 women) comparing prophylaxis with LMWH[158,159] or UFH[160,161] with placebo. There was no statistically significant difference between groups with respect to symptomatic VTE for LMWH vs placebo (two of 105 and zero of 105, respectively; RR, 2.97; 95% CI, 0.31-28.03) and UFH vs placebo (three of 297 and four of 333, respectively; RR, 0.85; 95% CI, 0.19-3.76).[157] However, the small number of study participants and outcome events provide insufficient evidence on which to make prophylaxis recommendations. A decision analysis model suggested that the benefits of LMWH prophylaxis exceed risks after cesarean section[141] but that this benefit was small in women with no risk factors and the low-quality evidence makes the assumptions that underlie the model questionable.

We use indirect evidence from patients undergoing general surgery[156] to generate anticipated absolute effects of LMWH on VTE and major bleeding events in pregnant women undergoing cesarean section. Table 4 and Table S12 show the quality of evidence and main findings from a meta-analysis of three trials comparing LMWH vs placebo in 4,890 patients undergoing general surgery.[162] We have rated down the quality of evidence because of indirectness. Extrapolating from general surgery patients (Table 4, Table S12), the balance of desirable and undesirable consequences would suggest prophylaxis for women with an absolute VTE risk of ≥ 30 of 1,000. With a baseline risk of five of 1,000 VTE after cesarean delivery, the presence or absence of risk factors will determine the absolute benefit of thrombosis prophylaxis. We categorize women into low risk (five of 1,000) and high risk (30 of 1,000); clinicians can use Table 3 to determine to which group their patient belongs.

Mechanical prophylaxis with elastic stockings or intermittent pneumatic compression are alternatives to pharmacologic prophylaxis in pregnant women at high risk of VTE and may be used with LMWH in women at particularly high risk of VTE. We consider evidence from a variety of populations undergoing general surgery to be applicable to pregnant women undergoing cesarean section and, therefore, refer the reader to Gould et al[156] in these guidelines for a detailed review of the evidence supporting the use of mechanical thromboprophylaxis with elastic stockings or intermittent pneumatic compression. In short, when compared with pharmacologic prophylaxis, mechanical prophylaxis is associated with less major bleeding (RR, 0.51; 95% CI, 0.40-0.64 for high-quality evidence) but a higher risk of VTE (RR, 1.8; 95% CI, 1.2-2.8 for low-quality evidence). Applying the baseline risk estimates for VTE and major bleeding events provided in Table 4 to 1,000 pregnant women at high risk of VTE after cesarean section, it follows that selecting mechanical prophylaxis over pharmacologic prophylaxis would result in 24 more VTE and seven fewer bleeding events. Although elastic stockings have been associated with skin breakdown when used poststroke (RR, 4.0; 95% CI, 2.4-6.9), this complication is much less likely to occur in young women. Elastic stockings and intermittent pneumatic compression may be inconvenient and cumbersome to use.

Table 4—*[Section 6.2.1-6.2.4] Summary of Findings: LMWH vs No Thromboprophylaxis for Prevention of VTE in Women Undergoing Cesarean Section*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects Over 6 wk Postpartum	
				Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE, DVT, and pulmonary embolism	4,890 (3 RCTs), 3 wk-9 mo	Moderate due to indirectness[b]	RR 0.29 (0.11-0.73)	Low risk (see Table 13)	
				5 VTE per 1,000[a]	3 fewer VTE per 1,000 (from 4 fewer to 1 fewer)
				High risk (see Table 13)	
				40 VTE per 1,000[a]	21 fewer per 1,000 (from 27 fewer to 9 fewer)
Major bleed[c]	5,456 (7 RCTs), 3 wk-9 mo	Moderate due to indirectness[c]	RR 2.03 (1.37-3.01)	20 bleeding events per 1,000[d]	20 more bleeding events per 1,000 (from 8 more to 40 more)

See Table 2 legend for expansion of abbreviations.

[a]Control group risk estimates come from studies providing risk factors for VTE after cesarean section (Tables S10 and S11).

[b]Rated down for indirect study population (general surgery patients). We did not rate down for risk of bias, although only five of eight RCTs of LMWH vs placebo/no treatment reported mortality.

[c]Rated down for indirectness due to variable bleeding definitions in trials: bleeding leading to death, transfusion, reoperation, or discontinuation of therapy. Measured at end of therapy.

[d]Control group risk estimate comes from a decision analysis by Blondon et al.[141]

The optimal duration of prophylaxis after cesarean section is not established. If we extrapolate from general surgery,[156,163-166] treatment until discharge from the hospital, with extended prophylaxis for those with significant ongoing risk factors, may be appropriate. We express a preference for LMWH over UFH because of its favorable safety profile (see section 4.0).

There are no relevant cost-effectiveness data in this setting using UFH or LMWH; however, in one study modeling the cost-effectiveness of intermittent pneumatic compression, this intervention was considered cost-effective when the incidence of post-cesarean section DVT was at least 6.8 of 1,000[167] (Tables S13, S14). However, these devices are not readily available at all sites, and patients and nurses often find them to be inconvenient and cumbersome to use.

Recommendations

6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B)**.**

6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors (Table 3), we suggest pharmacologic thromboprophylaxis (prophylactic LMWH), or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in the hospital following delivery rather than no prophylaxis (Grade 2B)**.**

Remarks: The reduced bleeding risk with mechanical prophylaxis should be weighed against the inconvenience of elastic stockings and intermittent pneumaric compression.

6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone (Grade 2C)**.**

6.2.4. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital (Grade 2C)**.**

7.0 Treatment of Proven Acute VTE During Pregnancy

PE remains a leading cause of maternal mortality in the western world,[168,169] and VTE in pregnancy is an important cause of maternal morbidity.[168,170,171] Results from studies in which either all or most patients underwent accurate diagnostic testing for VTE report that the incidence of VTE ranges from 0.6 to 1.7 episodes per 1,000 deliveries.[138,139,146,148,152,172] A meta-analysis showed that two-thirds of DVT occur antepartum, with these events distributed throughout all three trimesters.[173] In contrast, 43% to 60%

of pregnancy-related episodes of PE appear to occur in the 4 to 6 weeks after delivery.[139,148] Because the antepartum period is substantially longer than the 6-week postpartum period, the daily risk of PE, as well as DVT, is considerably higher following delivery than antepartum.

7.1 Treatment of VTE During Pregnancy

Based on safety data for the fetus, heparin compounds are preferred over vitamin K antagonists for the treatment of VTE in pregnancy (see section 3.0). LMWH is the preferred option for most patients because of its better bioavailability, longer plasma half-life, more predictable dose response, and improved maternal safety profile with respect to osteoporosis and thrombocytopenia (see section 2.0).[35-38] Further, LMWH is a more convenient option because it can be given once daily, and unlike UFH, LMWH does not require aPTT monitoring.[6]

A systematic review of LMWH use in pregnancy[38] and subsequent observational studies[36,150,174] confirm the safety and efficacy of LMWH in this patient population when used for treatment of VTE. Our strong recommendation for LMWH over vitamin K antagonists in the treatment of VTE in pregnancy is further supported by evidence showing that in the nonpregnant population, LMWH is more effective than vitamin K antagonists in preventing recurrent VTE and postthrombotic syndrome without increasing the risk of major bleeding events.[175-178] Table 5 and Table S15 summarize the quality of evidence and main findings from a systematic review of nonpregnant patients deemed applicable to the present population of pregnant women with acute VTE. Given these results, we consider the burden of self-injecting with LMWH for several months and possibility of skin reactions of lesser importance.

If LMWH is used for treatment of acute VTE in pregnancy, a weight-adjusted dosing regimen should be used. LMWH requirements may alter as pregnancy progresses because the volume of distribution of LMWH changes and glomerular filtration rate increases in the second trimester. The latter has led some to recommend a bid LMWH dosing schedule. However, many clinicians use a once-daily regimen to simplify administration and enhance compliance. Observational studies have not demonstrated any increase in the risk of recurrence with the once-daily regimen over the bid regimen.[150,174]

The need for dose adjustments over the course of pregnancy remains controversial. Some suggest that dose should be increased in proportion to the change in weight.[181] On the basis of small studies showing the need for dose-escalation to maintain therapeutic anti-Xa LMWH levels,[182,183] some advocate the performance of periodic (eg, every 1-3 months) antifactor Xa LMWH levels 4 to 6 h after injection with dose adjustment to maintain a therapeutic anti-Xa level (0.6-1.0 units/mL if a bid regimen is used and higher

Table 5—*[Section 7.1.2] Summary of Findings: Should LMWH Rather Than VKA Be Used for Long-term Treatment of VTE in Pregnant Women?*

				Anticipated Absolute Effects During Pregnancy[b]	
Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Risk With VKA	Risk Difference With LMWH (95% CI)
Recurrent symptomatic VTE, DVT, and pulmonary embolism	2496 (7 RCTs); median, 6 mo	Moderate due to risk of bias[a]	RR 0.62 (0.46-0.84)	30 VTE per 1,000[b]	11 fewer VTE per 1,000 (from 16 fewer to 5 fewer)
Major bleeding	2727 (8 RCTs); median, 6 mo	Moderate due to imprecision[c]	RR 0.81 (0.55-1.2)	20 bleeding events per 1,000[d]	4 fewer bleeding events per 1,000 (from 9 fewer to 4 more)
PTS self-reported leg symptoms and signs	100 (1 RCT); median, 3 mo	Low due to risk of bias[a] and indirectness[e]	RR 0.85 (0.77-0.94)	480 PTS per 1,000[f]	38 fewer bleeding events per 1,000 (from 110 fewer to 29 fewer)

Limited to LMWH regimens that used ≥ 50% of the acute treatment dose during the extended phase of treatment. Meta-analysis is based on RCTs as referenced in Kearon et al[178] in this guideline. PTS = postthrombotic syndrome; VKA = vitamin K antagonist. See Table 2 legend for expansion of other abbreviations.

[a]Risk of bias due to lack of blinding.

[b]Control group risk estimate for VTE with VKAs comes from cohort study by Prandoni et al,[179] adjusted to the 6-mo time frame considered applicable to the pregnancy period.

[c]Rated down for imprecision because CI includes both benefit and harm. Borderline decision not to rate down for risk of bias (considered this outcome less subjective, so lack of blinding not serious threat to validity).

[d]Control group risk estimate for major bleeding events comes from cohort studies by Prandoni et al[179] and Beyth et al,[180] adjusted to a 6-mo time frame considered applicable to the pregnancy period.

[e]Predictive value from 3 mo (follow-up in study) to long term is uncertain.

[f]Control group risk estimate for PTS comes from observational study of pregnant women (most mild).[171]

if a once-daily regimen is chosen). However, other researchers have demonstrated that few women require dose adjustment when therapeutic doses of LMWH are used.[184-186] Given the absence of large studies using clinical end points that demonstrate an optimal therapeutic anti-Xa LMWH range or that dose adjustments increase the safety or efficacy of therapy, the lack of accuracy and reliability of the measurement,[187] the lack of correlation with risk of bleeding and recurrence,[188] and the cost of the assay, routine monitoring with anti-Xa levels is difficult to justify.

Where LMWH cannot be used or when UFH is preferred (eg, in patients with renal dysfunction), UFH can be used through one of two alternatives: (1) initial IV therapy followed by adjusted-dose subcutaneous UFH given every 12 h or (2) bid adjusted-dose subcutaneous UFH. With subcutaneous therapy, UFH doses should be adjusted to prolong a midinterval (6 h postinjection) aPTT into therapeutic range, although it is recognized that aPTT monitoring is less reliable in pregnancy.[6] As previously discussed, the use of fondaparinux is inadvisable in pregnancy (see section 3.5). In this guideline, Linkins et al[14] and Kearon et al[178] present evidence regarding platelet count monitoring for the detection of HIT and the role of compression stockings in the acute management of DVT.

It remains unclear whether the dose of LMWH (or UFH) can be reduced after an initial phase of therapeutic anticoagulation. Some suggest that full-dose anticoagulation should be maintained throughout pregnancy and the puerperium because of the ongoing risk of recurrent VTE. However, regimens in which the intensity of LMWH is reduced later during the course of therapy to an intermediate-dose regimen[26] or 75% of a full-treatment dose[177] have been used successfully in the nonpregnant population, including in cancer patients who have a much higher risk of recurrence. A similar approach when using LMWH in pregnancy may reduce the small risks of anticoagulant-related bleeding and heparin-induced osteoporosis. Although there have been no studies directly comparing full-dose LMWH with one of these modified dosing strategies in pregnant women, a modified dosing regimen may be useful in pregnant women at increased risk of either of these two complications.

No studies have assessed optimal duration of anticoagulant therapy for treatment of pregnancy-related VTE. In nonpregnant patients with VTE, evidence supports a minimum duration of 3 months treatment (see Kearon et al[178] in this guideline). We consider the additional fivefold to 10-fold increase in risk for VTE in pregnant women, coupled with the high rate of proximal thrombi (compared with the nonpregnant population), sufficient to recommend treatment throughout pregnancy and the postpartum period for a minimum total duration of 3 months.

The delivery options in women using anticoagulants are best considered by a multidisciplinary team. Several options are possible, including spontaneous labor and delivery, induction of labor, and elective cesarean section. The plan for delivery should take into account obstetric, hematologic, and anesthetic issues. In order to avoid an unwanted anticoagulant effect during delivery (especially with neuraxial anesthesia) in women receiving adjusted-dose subcutaneous UFH[11] or LMWH who have a planned delivery; twice-daily subcutaneous UFH or LMWH should be discontinued 24 h before induction of labor or cesarean section, whereas patients taking once-daily LMWH should take only 50% of their dose on the morning of the day prior to delivery (see Kunz et al[189] in this guideline). If spontaneous labor occurs in women receiving anticoagulation, neuraxial anesthesia should not be used. Where the level of anticoagulation is uncertain and where laboratory support allows for rapid assessment of heparin levels, then testing can be considered to guide anesthetic and surgical management. In women receiving subcutaneous UFH, careful monitoring of the aPTT is required and, if it is markedly prolonged, protamine sulfate[190] may be required to reduce the risk of bleeding. If bleeding occurs that is considered secondary to LMWH rather than to an obstetric cause, protamine sulfate may provide partial neutralization.[191]

Women with a very high risk for recurrent VTE (eg, proximal DVT or PE close to the expected date of delivery) may benefit by having a planned delivery by induction or cesarean section, as appropriate, so that the duration of time without anticoagulation can be minimized. Those at the highest risk of recurrence (eg, proximal DVT or PE within 2 weeks) can be switched to therapeutic IV UFH, which is then discontinued 4 to 6 h prior to the expected time of delivery or epidural insertion. Alternatively, a temporary inferior vena caval filter can be inserted and removed postpartum. However, the latter may be best restricted to women with proven DVT who have recurrent PE despite adequate anticoagulation because experience with these devices during pregnancy is limited,[192-194] and the risk of filter migration and inferior vena cava perforation may be increased during pregnancy.[193,194]

Recommendations

7.1.1. For pregnant women with acute VTE, we recommend therapy with adjusted-dose subcutaneous LMWH over adjusted-dose UFH (Grade 1B)**.**

7.1.2. For pregnant women with acute VTE, we recommend LMWH over vitamin K antagonist treatment antenatally (Grade 1A)**.**

7.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C)**.**

7.1.4. For pregnant women receiving adjusted-dose LMWH or UFH therapy and where delivery is planned, we recommend discontinuation of the heparin at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B)**.**

8.0 Prevention of VTE in Pregnant Women With Prior DVT or PE

Compared with individuals without a history of VTE, patients with previous events are at increased risk of future episodes of DVT and PE.[195] Women with a history of VTE have a threefold to fourfold higher risk of VTE during subsequent pregnancies than outside pregnancy.[196] Thromboprophylaxis during pregnancy involves long-term parenteral LMWH, which is expensive, inconvenient, and painful to administer. Although bleeding, osteoporosis, and HIT are very uncommon in patients receiving prophylactic LMWH,[37-40,197] injection site skin reactions may occur.[45] The threshold for recommending postpartum prophylaxis is lower than for antepartum prophylaxis because of the shorter length of required treatment (ie, 6 weeks) and the higher average daily risk of VTE in the postpartum period.[137,173] Given the distribution of DVT throughout all three trimesters,[173] antepartum prophylaxis, if used, should be instituted early in the first trimester.

8.1 Prior VTE and Pregnancy

Cohort studies evaluating the risk of recurrent VTE during pregnancy in women with a history of VTE in whom no prophylaxis is given have shown variable results (Table S16). The higher risk estimates from retrospective studies of nonconsecutive patients in which objective testing was not used routinely to confirm the diagnosis of recurrent VTE likely represent overdiagnosis.[198,199] Prospective studies provide lower estimates.[200-203]

The largest prospective study to date investigated 125 pregnant women with a single previous episode of objectively diagnosed VTE in whom antepartum heparin was withheld and anticoagulants (usually warfarin with a target INR of 2.0-3.0 with an initial short course of UFH or LMWH) were given in the postpartum period for 4 to 6 weeks.[203] In this study, the incidence of antepartum recurrence was 2.4% (95% CI, 0.2%-6.9%), whereas that during the postpartum period was 2.5% (95% CI, 0.5%-7.0%). The advanced median gestational age at enrollment (~15 weeks) and the exclusion of women with known thrombophilia might have resulted in an underestimation of the risk of pregnancy-related recurrent VTE.

In subsequently published large retrospective cohort studies, the probability of antepartum VTE in women not given prophylaxis was ~6%, whereas for postpartum VTE, the observed incidence ranged from 6% to 8%.[204,205] Differences in study population (inclusion of women with more than one prior episode of VTE and inclusion of pregnancies not ending in live birth [ie, miscarriages]) and failure to independently adjudicate recurrent events might account for the higher risk of recurrence. However, as shown in Table S16, the overall risk of recurrent VTE antepartum in both prospective and retrospective studies was <10%, and CIs around the risk estimates of individual studies are overlapping.

Data regarding prognostic factors for recurrent VTE during pregnancy are inconsistent. A post hoc subgroup analysis of the prospective cohort study described previously identified women without thrombophilia who had a temporary risk factor (including oral contraceptive therapy or pregnancy) at the time of their prior VTE event as being at low risk of recurrence, with no recurrent events in 44 patients (0%; 95% CI, 0.0%-8.0%).[203] Antepartum recurrences occurred in three of 51 women with abnormal thrombophilia testing, a previous episode of thrombosis that was unprovoked, or both (5.9%; 95% CI, 1.2%-16.0%).

In the retrospective studies, the association between the presence or absence of temporary risk factors or of a definable thrombophilia and the risk of recurrent VTE associated with pregnancy was not consistent (Table S16). In these studies, it appears that women who had their first episode of VTE provoked by use of oral contraceptives or related to pregnancy or the postpartum period had a higher risk of recurrent VTE in a subsequent pregnancy than women whose first VTE was unprovoked or associated with a nonhormonal transient risk factor, although these differences did not reach statistical significance in the individual studies.[204,205] These findings are consistent with those from a large population-based cohort study that used administrative data[206] in which women who had their first VTE associated with pregnancy or the postpartum period had a higher risk of recurrence

during a subsequent pregnancy than women with an unprovoked first VTE (ie, 4.5% vs 2.7%; RR, 1.71; 95% CI, 1.0-2.8).

8.2 Prevention of Recurrent VTE in Pregnant Women

A systematic review of the effects of thromboprophylaxis in pregnant women[157] identified two randomized controlled trials that evaluated the safety and efficacy of prophylaxis (compared with placebo or no treatment) in pregnant women with prior VTE.[158,202] Both studies have major methodologic weaknesses, including very small sample sizes (n = 40 and n = 16).[158,202] A third, unblended randomized trial compared LMWH prophylaxis with UFH prophylaxis in a selected group of pregnant women with prior VTE[207] (Table S17).

Several observational studies have evaluated the risk of recurrent VTE with various treatment regimens[36-38,44,199,204,208-212] (Table S18). Some of these studies stratified patients according to their perceived risk of recurrence. The estimates of the risk of recurrent VTE while using some form of pharmacologic prophylaxis range from 0% to 15%, with the higher results seen in an older study that may have overestimated the recurrence rate because objective diagnostic testing was not used.[199]

Given the low quality of the direct evidence, we use indirect evidence about the relative effects of thromboprophylaxis from other patient populations to inform our recommendations for antenatal prevention of VTE. Table 6 and Table S19 summarizes the quality of the evidence and main findings from a systematic review of thromboprophylaxis in orthopedic patients at high risk for VTE.[136] Our choice of indirect evidence is based on similarities in risk of VTE, the type and duration of intervention (extended prophylactic-dose LMWH), and outcomes (symptomatic VTE and major bleeding events). Our baseline risk estimates are based on observational studies of pregnant women with previous VTE (Table S16). We have categorized patients into groups at low risk (major transient risk factor for VTE), intermediate (hormone- or pregnancy-related or unprovoked VTE), or high risk (multiple prior unprovoked VTE or persistent risk factors, such as paralysis) during pregnancy. Clinicians can use these risk groups to determine the anticipated absolute effects of treatment with LMWH in their patients. Given the evidence of similar absolute risks for VTE antepartum and postpartum outlined

Table 6—*[Section 8.2.2, 8.2.3] Summary of Findings: Antepartum and Postpartum Prevention of VTE With Prophylactic-Dose LMWH vs No Prophylaxis in Pregnant Women With Prior VTE*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects During Pregnancy	
				Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE, DVT, and pulmonary embolism	1,953 (6 RCTs), 27-35 d postoperative	Low due to indirectness[c] and imprecision[a]	RR 0.36 (0.20-0.67)	Low risk (transient risk factor)	
				20 VTE per 1,000[a]	13 fewer VTE per 1,000 (from 16 fewer to 7 fewer)
				Intermediate and high risk (pregnancy- or estrogen-related, idiopathic or multiple prior VTE but discontinued VKAs)	
				80 VTE per 1,000[a]	51 fewer VTE per 1,000 (from 65 fewer to 30 fewer)
Major bleeding[b]	1,953 (6 RCTs), 27-35 d postoperative	Low due to indirectness[c] and imprecision[d]	RR 0.43 (0.11-1.65)	Antepartum period	
				5 bleeding events per 1,000[e]	No significant difference; 3 fewer bleeding events per 1,000 (from 3 fewer to 3 more)
				Postpartum period	
				20 bleeding events per 1,000[e]	No significant difference; 11 fewer bleeding events per 1,000 (from 18 fewer to 13 more)

See Table 2 and 5 legends for expansion of abbreviations.

[a]Control group risk estimates for VTE in the antepartum and postpartum period come from studies summarized in Table S16. Quality of evidence is rated down because of imprecision in these risk estimates. We consider the distribution of VTE antepartum and postpartum to be equal.

[b]Nonfatal maternal hemorrhage (according to section 1.0) defined as a symptomatic bleeding complication noted during pregnancy or within 6 wk postpartum that involved bleeding into a critical site, bleeding causing a fall in hemoglobin level of ≥ 2 g/dL, or bleeding leading to transfusion of ≥ 2 units of whole blood or red cells.

[c]Population is indirect (ie, did not include pregnant women). Different doses of LMWH were used. Treatment was initiated variably before or after surgery with a duration of ~7 days (in hospital). Outcomes variably reported. Meta-analysis also provides other outcomes such as mortality, asymptomatic DVT, and specific bleed outcomes (wound hematoma, transfusion). Follow-up varied between trials from 3 wk to 9 mo.

[d]Wide CIs for absolute effect of LMWH in high-risk group included benefit and harm.

[e]Control group risk estimate for major bleeding events comes from a systematic review by Greer et al.[38]

previously herein, the absolute effects of LMWH shown in Table 6 and Table S19 are applicable both to the 9-month antepartum period and the 6-week postpartum period.

LMWH is the preferred agent for prophylaxis (see section 2.0). Dose regimens include subcutaneous enoxaparin 40 mg every 24 h,[27,158] dalteparin 5,000 units every 24 h,[207] and dose-adjusted LMWH to achieve a peak anti-Xa level of 0.2 to 0.6 units/mL[213-215] (Table S18). Although all of the studies evaluating these regimens reported low recurrence rates, most were cohort studies and, therefore, no comparative data from untreated controls are available. Further, because different doses of anticoagulant prophylaxis have not been compared directly, the optimal dose of LMWH is unknown. Although indirect evidence (Table 6, Table S19) suggests that prophylactic-dose LMWH is effective (ie, RR of 0.36) in high-risk settings, some investigators have reported recurrent pregnancy-associated VTE in pregnant women prescribed prophylactic LMWH[36,37,204,208,216] However, it is unclear whether these represent true failures or were due to compliance issues with long-term daily subcutaneous injections.

Women who have an indication for long-term vitamin K antagonists, mostly because of multiple episodes of VTE, are considered at very high risk of recurrent VTE during pregnancy and the postpartum period. Dose-adjusted LMWH is a rational option for anticoagulant therapy during pregnancy, with resumption of long-term vitamin K antagonists after delivery. Alternatively, a reduced therapeutic-dose regimen (~75% of the usual therapeutic dose) may represent a reasonable option given evidence of the superior effectiveness of LMWH compared with vitamin K antagonists observed in the treatment of VTE in cancer patients.[177]

Increased renal clearance of LMWH during pregnancy has led to suggestions that clinicians monitor the anticoagulant effect of prophylactic-dose LMWH using anti-Xa levels.[209,214] However, the appropriate target range for prophylaxis is uncertain, and there is no evidence to support any specific target range. Moreover, routine monitoring of anti-Xa levels is expensive, inconvenient, and possibly unreliable[187,217] (see Garcia et al[188] in this guideline).

An alternate strategy for DVT prevention is repeated screening during the antepartum period with noninvasive tests for DVT, such as compression ultrasonography. This strategy generally is not justified for two reasons. First, if we postulate rates of recurrent VTE of 5%, given an ultrasound sensitivity of 96% and specificity of 98%, we would anticipate that 28% of positive results would be false positives. Second, there is no evidence to guide the timing of screening, and it is possible that a clinically important recurrence could occur between ultrasounds. We recommend that women should be investigated aggressively if symptoms suspicious of DVT or PE occur. That said, the performance of a baseline compression ultrasound of a previously affected leg prior to or early on in pregnancy may be useful to help differentiate residual thrombosis from new disease in women presenting with symptoms during pregnancy (see Bates et al[218] in this guideline).

Recommendations

8.2.1. For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

8.2.2. For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).

8.2.3. For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

8.2.4. For pregnant women receiving long-term vitamin K antagonists, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum rather than prophylactic-dose LMWH (Grade 2C).

9.0 Prevention of VTE in Pregnant Women With Thrombophilia and No Prior VTE

9.1 Risk of Pregnancy-Related VTE in Women With Thrombophilia

A number of studies have examined the association between hereditary thrombophilias and pregnancy-related VTE. Table 7 presents estimated and observed pooled risks for pregnant women with thrombophilia in the absence and presence of a positive family history.

In a systematic review of nine studies that assessed the risk of VTE in pregnant women with inherited thrombophilias but not necessarily a family history of

Table 7—*[Section 9.2.1-9.2.4] Risk of Pregnancy-Related VTE in Women With Thrombophilia Stratified by Family History for VTE*

Thrombophilic Defect, n/No. Women With Thrombophilia	Estimated Relative Risk, OR (95% CI)[a]	Observed or Estimated Absolute Risk of VTE Antepartum and Postpartum Combined, % Pregnancies (95% CI)[b,c]
Antithrombin/protein C/protein S deficiency combined		
Family studies, 7/169[219]	…	4.1 (1.6-8.3)
Antithrombin deficiency		
Family studies, 1/33[219]	…	3.0 (0.08-15.8)
Nonfamily studies, 8/11[151]	4.7 (1.3-17.0)	0.7 (0.2-2.4)
Protein C deficiency		
Family studies, 1/60[219]	…	1.7 (0.4-8.9)
Nonfamily studies, 23/32[151]	4.8 (2.2-10.6)	0.7 (0.3-1.5)
Protein S deficiency		
Family studies, 5/76[219]	…	6.6 (2.2-14.7)
Nonfamily studies, 16/28[151]	3.2 (1.5-6.9)	0.5 (0.2-1.0)
Factor V Leiden, heterozygous		
Family studies, 26/828[220-222, 223]	…	3.1 (2.1-4.6)
Nonfamily studies, 96/226[151]	8.3 (5.4-12.7)	1.2 (0.8-1.8)
Factor V Leiden, homozygous		
Family studies, 8/57[224-226]	…	14.0 (6.3-25.8)
Nonfamily studies, 29/91[153]	34.4 (9.9-120.1)	4.8 (1.4-16.8)
Prothrombin G20201A mutation, heterozygous		
Family studies, 6/228[227,228]	…	2.6 (0.9-5.6)
Nonfamily studies, 42/61[151]	6.8 (2.5-18.8)	1.0 (0.3-2.6)
Prothrombin G20201A mutation, homozygous		
Family studies, n/a	…	…
Nonfamily studies, 2/2[151]	26.4 (1.2-559.3)	3.7 (0.2-78.3)

[a]Data from Robertson et al[151]; number of VTE cases in women with the thrombophilia in question vs VTE cases in women without the specified thrombophilia.

[b]In the family studies, number of women with VTE out of number of women with thrombophilia. Observed absolute risks for family studies are risks observed in cohorts of families from a proband with symptomatic VTE and thrombophilia. Study numbers are pooled. Incidence is derived by adding number of events and dividing by number of pregnancies.

[c]Estimated absolute risks for nonfamily studies are derived by multiplying the pooled ORs with their corresponding 95% CIs from Robertson et al[151] with the overall baseline VTE incidence (ie, antepartum and until 6 wk postpartum combined) of 1.40 per 1,000 from a group of women aged 25 to 34 y (I. A. Greer, MD, personal communication, November 2010).

VTE, all with the exception of homozygosity for the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T) were associated with a statistically significant increase in the risk of pregnancy-related VTE (Table 7).[151] The highest risks were associated with homozygosity for factor V Leiden (OR, 34.4; 95% CI, 9.9-120.1) or the prothrombin G20210A variant (OR, 26.4; 95% CI, 1.2-559.3). The most common inherited thrombophilias (ie, heterozygosity for factor V Leiden [OR, 8.3; 95% CI, 5.4-12.7], prothrombin G20210A variant [OR, 6.8; 95% CI, 2.5-18.8]) were associated with lower risks. Deficiencies of the endogenous anticoagulants were associated with similar risk increases (ORs for antithrombin, protein S, and protein C deficiency, 4.7 [95% CI, 1.30-17.0], 4.8 [95% CI, 2.2-10.7], and 3.2 [95% CI, 1.5-6.0], respectively).

In a subsequently published meta-analysis undertaken to provide an estimate of the association of the factor V Leiden mutation with pregnancy-related VTE that used slightly different study entry criteria, the risk estimate obtained from case-control studies was similar to that in the first systematic review (OR, 8.6; 95% CI, 4.8-12.6).[229] However, cohort studies, which are likely to be more reliable, showed a lower pooled OR of 4.5 (95% CI, 1.8-10.9).[229] Given a background incidence of VTE during pregnancy of ~1/1,000 deliveries, the absolute risk of VTE in women without a prior event or family history remains low (in the range of 5-12/1,000 deliveries) for most of the inherited thrombophilias, except perhaps for homozygous carriers of the factor V Leiden or the prothrombin mutations where the OR from case-control studies suggest baseline risks of pregnancy-related VTE of ~4%.

Regardless of the presence of thrombophilia, a positive family history of VTE increases the risk for VTE twofold to fourfold.[230] Several family-based cohort studies found that women with inherited thrombophilia and a positive family history who have not had a previous episode of VTE have a risk of developing a first VTE during pregnancy or the postpartum period of between 1.7% for protein C deficiency[219] and 14.0% for homozygous carriers of the factor V

Leiden mutation[224-226] (Table 7).[219-228,231,232] These estimates are, however, imprecise, particularly for the less common thrombophilias (see wide CIs in Table 7).

Although the deficiencies of the natural anticoagulants (and in particular, antithrombin deficiency) are usually labeled as high-risk thrombophilias, this perception is based on older studies with important methodological limitations. For instance, Conard et al[233] reported a very high risk of pregnancy-related VTE in women with antithrombin and protein C or protein S deficiency, but many patients included in this report had a history of recurrent VTE, and all episodes of VTE were not objectively confirmed. More rigorous recent studies included in Table 7 do not support the high risk of recurrence from previous studies. Two small studies that investigated the risk in women with both the factor V Leiden and prothrombin mutations found similar risk estimates to those seen in single heterozygous carriers.[226,234] Based on these estimates, we suggest that serious consideration of prophylaxis is warranted only in (1) homozygous carriers of the factor V Leiden or prothrombin gene mutations (regardless of family history) and (2) women with the other inherited thrombophilias with a family history of VTE.

Acquired thrombophilias have been less well studied, but repeated positivity at least 12 weeks apart for APLAs (lupus anticoagulants [nonspecific inhibitors], moderate- or high-titer IgG or IgM anticardiolipin antibodies [> 40 GPL or MPL or > 99th percentile], or moderate- of high-titer IgG or IgM anti-β_2-glycoprotein I antibodies [> 99th percentile]) is associated with an increased risk of VTE.[235,236] The VTE risk in women with APLAs and no previous venous thrombosis is uncertain.[237,238]

Hyperhomocysteinemia is associated with an increased risk of VTE in nonpregnant women.[239] However, it does not appear that homozygosity for MTHFR C667T (the genetic abnormality most commonly associated with hyperhomocysteinemia) alone leads to an increased risk of VTE in pregnant women.[151] As clinical events in homozygotes are likely to reflect the interaction of the genotype with a relative deficiency of vitamins, such as B12 and folic acid, the absence of an association of this genotype with gestational VTE may reflect pregnancy-related physiological reduction in homocysteine levels and the effects of folic acid supplements that are now taken widely by women in pregnancy for prevention of neural tube defects.[240]

9.2 Prevention of Pregnancy-Related VTE in Women With Thrombophilia

Because of a paucity of high-quality evidence measuring the effectiveness and safety of antithrombotic agents in preventing VTE in this population, we used indirect evidence to inform our treatment recommendations. Given the low risk for VTE in women with thrombophilia but no family history, we restricted our analysis to women with thrombophilia and a family history of VTE (Table 8, Table S20). We estimated the baseline VTE incidence (ie, antepartum and until 6 weeks postpartum combined) as 1.40 of 1,000 (I. A. Greer, MD, personal communication, November 8, 2010). Evidence about relative effects of treatment is taken from a meta-analysis of thromboprophylaxis in patients undergoing hip arthroplasty.[136] We have rated the quality of evidence as low because of indirectness of the population and intervention as well as the considerable imprecision in baseline risk estimates for VTE in women with thrombophilias.

Estimates of absolute effects are relatively large in women with a positive family history of VTE who are homozygous for the factor V Leiden mutation—47 fewer VTE/1,000 antepartum and 47 fewer VTE of 1,000 postpartum when prophylaxis is used, with no increased risk of major bleeding (Table 8, Table S20). In women with a positive family history for VTE and antithrombin, protein C, or protein S deficiency, these figures are approximately 13 of 1,000 antepartum and 13 of 1,000 postpartum. For the other thrombophilias, the estimated number of VTE prevented is 10 of 1,000 both antepartum and postpartum. The evidence is, however, low quality and includes imprecise estimates.

The increased risk in women with thrombophilia and a family history of VTE begins early in pregnancy[173]; therefore, when antepartum prophylaxis is used, it should be commenced as early as possible in the first trimester. The burden of self-injecting with LMWH over several months and the risk of skin reactions weigh into our weak recommendation for antepartum thromboprophylaxis. For postpartum prophylaxis, we consider vitamin K antagonist therapy targeted to an INR of 2.0 to 3.0 an appropriate alternative to LMWH, except in patients with protein C or S deficiency who are at risk for developing warfarin-induced skin necrosis.[241-243]

Recommendations

9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B)**.**

Table 8—*[Section 9.2.1-9.2.4] Summary of Findings: Antepartum and Postpartum Prophylactic-Dose LMWH vs No Thromboprophylaxis for Pregnant Women With a Known Thrombophilia*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects Antepartum and Postpartum (Different Risk Estimates for Bleeding Events)	
				Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE, DVT, and pulmonary embolism	1,953 (6 RCTs), 27-35 d postoperative	Low due to indirectness[b] and imprecision[a]	RR 0.36 (0.20-0.67)	Positive family history VTE and heterozygous factor V Leiden or prothrombin 202010A	
				15 VTE per 1,000[c]	10 fewer VTE per 1,000 (from 12 fewer to 5 fewer)
				Positive family history VTE and antithrombin, protein C, or protein S deficiency	
				20 VTE per 1,000[c]	13 fewer VTE per 1,000 (from 16 fewer to 6 fewer)
				Positive family history VTE and homozygous factor V Leiden or prothrombin 20210A	
				70 VTE per 1,000[c]	47 fewer per 1,000 (from 56 fewer to 31 fewer)
				No family history of VTE but homozygous factor V Leiden or prothrombin 20210A	
				20 VTE per 1,000[c]	13 fewer VTE per 1,000 (from 16 fewer to 6 fewer)
Major bleeding	5,456 (7 RCTs), 3 wks-9 mo	Moderate due to indirectness[b]	RR 0.43 (0.11-1.65)	Antepartum period	
				5 bleeding events per 1,000[d]	No significant difference; 3 fewer bleeding events per 1,000 (from 3 fewer to 3 more)
				Postpartum period	
				20 bleeding events per 1,000[d]	No significant difference; 11 fewer bleeding events per 1,000 (from 18 fewer to 13 more)

See Table 2 legend for expansion of abbreviations.

[a]Imprecision in control group risk estimates for all thrombophilias (see Table S20) results in imprecise anticipated absolute effects.

[b]The population did not include pregnant women. Different doses of LMWH were used; treatment was initiated variably before or after surgery with a duration of ~7 days in hospital and 25 d out of hospital. Outcomes were variably reported.

[c]Control group risk estimate for VTE comes from observational studies summarized in Table S20. Our antepartum risk estimate is based on assumed equal distribution of antepartum and postpartum VTE events based on data from observational studies (I. A. Greer, MD, personal communication, November 8, 2010).

[d]Control group risk estimate for major bleeding events antepartum comes from systematic review by Greer.[38]

9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C)**.**

9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B)**.**

9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C)**.**

10.0 Thrombophilia and Pregnancy Complications

Various pregnancy complications have been linked to thrombophilic states. Unfortunately, adverse pregnancy outcomes are not infrequent in the general population. Fifteen percent of clinically recognized pregnancies end in miscarriage, but total reproductive loss may be as high as 50%.[244] Five percent of women experience two or more losses, and 1% to 2% have three or more consecutive losses. Other placental-mediated pregnancy complications include preeclampsia, fetal growth restriction, and placental abruption.

Successful pregnancy outcome depends on trophoblast invasion into the uterine vasculature and on the development and maintenance of an adequate uteroplacental circulatory system. Inadequate placentation and damage to the spiral arteries with impaired flow, an increased maternal inflammatory response, and prothrombotic changes may lead to placental-medicated pregnancy complications.[245] Animal studies suggest that the hemostatic system plays an important role in placental and fetal development, although hypercoagulability is unlikely to be the sole mechanism by which thrombophilia increases the risk of pregnancy failure. It is more likely that effects on trophoblast differentiation and early placentation may be involved through as yet unknown mechanisms. Interestingly, both aspirin and heparin appear to influence these early trophoblast and placentation mechanisms in vitro as well as in a hypercoagulability mouse model.[246-248]

10.1 Risk of Pregnancy Complications in Women With Thrombophilia

Pregnancy complications occur with increased frequency in women with APLAs. APLA syndrome can be diagnosed in women who test positive for lupus anticoagulant (nonspecific inhibitor) or moderate- to high-titer antibodies to IgG or IgM anticardiolipin (> 40 GPL or MPL or > 99th percentile) or IgG or IgM β_2-glycoprotein I (> 99th percentile) on two occasions at least 12 weeks apart and who experience at least one unexplained fetal death (later than 10 weeks of gestation); three or more unexplained consecutive miscarriages (before 10 weeks of gestation); or one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency.[235]

There is convincing evidence that APLAs are associated with an increased risk of recurrent and late pregnancy loss.[151,249-253] Lupus anticoagulants (nonspecific inhibitors) are more strongly related to pregnancy loss than are the other antibodies against phospholipids; although associations have also been seen with moderate- to high-titer IgG and IgM antibodies (> 5 SDs above normal, > 99th percentile, or > 20 GPL/MPL units).[253] The importance of anti-β_2-glycoprotein I antibodies is not clearly established.[253] Furthermore, there is less agreement on the association between the presence of APLAs and the occurrence of other pregnancy complications, including preeclampsia, placental abruption, and intrauterine growth restriction.[151,243,254-268]

The association between inherited thrombophilic disorders and miscarriage, first observed in women from families with venous thrombosis, has been confirmed in many studies.[151,228,269-277] A single late fetal loss and severe preeclampsia are also associated with inherited thrombophilia,[151,274,275] whereas the presence of an association is controversial in women with fetal growth restriction or placental abruption.[151,277]

Table 9 summarizes the findings of a meta-analysis of 25 studies (predominantly case control)[151] examining the association between thrombophilia and various pregnancy complications. The wide CIs around the point estimates of some associations illustrate the uncertainty of the findings, particularly for the less-prevalent thrombophilias. In a meta-analysis limited to prospective cohort studies,[277] the pooled OR for pregnancy loss in women with factor V Leiden (absolute risk, 4.2%) compared with women without this mutation (absolute risk, 3.2%) was 1.52 (95% CI, 1.06-2.19). The meta-analysis was unable to establish or refute an association between the presence of factor V Leiden and preeclampsia (OR, 1.23; 95% CI, 0.89-1.70) or fetal growth restriction (OR, 1.0; 95% CI, 0.80-1.25). Results also failed to demonstrate or exclude an association between the prothrombin mutation and either preeclampsia (OR, 1.25; 95% CI, 0.79-1.99), fetal growth restriction (OR, 1.25; 95% CI, 0.92-1.70), or pregnancy loss (OR, 1.13; 95% CI, 0.64-2.01). Given these results, it remains unclear whether screening for inherited thrombophilias is in the best interests of women with pregnancy complications.

10.2 Prevention of Pregnancy Complications in Women With Thrombophilia

Clinicians are increasingly using antithrombotic therapy in women at risk for these complications (Tables S21, S22).[278-299] With respect to acquired thrombophilias, of the interventions examined in a systematic review[252] (up to date in February 2005) that summarized the data from 13 randomized or quasi-randomized trials, including a total of 849 pregnant women with APLA and a history of at least two unexplained pregnancy losses, only UFH combined with aspirin (two trials, n = 150) reduced the incidence of pregnancy loss.[278,279] Consistent findings of a third study (n = 72),[290] when included, yielded an relative risk of 0.44 (95% CI, 0.30-0.66) for UFH combined with aspirin compared with aspirin alone (Table 10, Table S23). The use of higher-dose UFH and aspirin did not decrease the risk of pregnancy loss compared with low-dose UFH and aspirin (one trial, n = 50; RR, 0.83; 95% CI, 0.29-2.38).[252,280] On its own, aspirin (three trials, n = 71) failed to demonstrate or exclude an effect on pregnancy loss compared with usual care[281] or placebo[282,283] (RR, 1.05; 95% CI, 0.66-1.68).[252] In one trial, the combination of LMWH with aspirin had also failed to demonstrate or exclude an effect on pregnancy loss when compared with

Table 9—*[10.2.1,10.2.2] Association Between Pregnancy Complications and Thrombophilia*

Type of Thrombophilia	Early Loss	Recurrent First Trimester Loss	Nonrecurrent Second Trimester Loss	Late Loss	Preeclampsia	Placental Abruption	Fetal Growth Restriction
Factor V Leiden (homozygous)	2.71 (1.32-5.58)	[a]	[a]	1.98 (0.40-9.69)	1.87 (0.44-7.88)	8.43 (0.41-171.20)	4.64 (0.19-115.68)
Factor V Leiden (heterozygous)	1.68 (1.09-2.58)	1.91 (1.01-3.61)[a]	4.12 (1.93-8.81)[a]	2.06 (1.10-3.86)	2.19 (1.46-3.27)	4.70 (1.13-19.59)	2.68 (0.59-12.13)
Prothrombin gene mutation (heterozygous)	2.49 (1.24-5.00)	2.70 (1.37-5.34)	8.60 (2.18-33.95)	2.66 (1.28-5.53)	2.54 (1.52-4.23)	7.71 (3.01-19.76)	2.92 (0.62-13.70)
MTHFR C677T (homozygous)	1.40 (0.77-2.55)	0.86 (0.44-1.69)	NA	1.31 (0.89-1.91)	1.37 (1.07-1.76)	1.47 (0.40-5.35)	1.24 (0.84-1.82)
Antithrombin deficiency	0.88 (0.17-4.48)	NA	NA	7.63 (0.30-196.36)	3.89 (0.16-97.19)	1.08 (0.06-18.12)	NA
Protein C deficiency	2.29 (0.20-26.43)	NA	NA	3.05 (0.24-38.51)	5.15 (0.26-102.22)	5.93 (0.23-151.58)	NA
Protein S deficiency	3.55 (0.35-35.72)	NA	NA	20.09 (3.70-109.15)	2.83 (0.76-10.57)	2.11 (0.47-9.34)	NA
Anticardiolipin antibodies	3.40 (1.33-8.68)	5.05 (1.82-14.01)	NA	3.30 (1.62-6.70)	2.73 (1.65-4.51)	1.42 (0.42-4.77)	6.91 (2.70-17.68)
Lupus anticoagulants (nonspecific inhibitor)	2.97 (1.03-9.76)	NA	14.28 (4.72-43.20)	2.38 (0.81-6.98)	1.45 (0.70-4.61)	NA	NA
Hyperhomocysteinemia	6.25 (1.37-28.42)	4.21 (1.28-13.87)	NA	0.98 (0.17-5.55)	3.49 (1.21-10.11)	2.40 (0.36-15.89)	NA

Data are presented as OR (95% CI) and derived from Robertson et al.[151] MTHFR = methylene tetrahydrofolate reductase variant; NA = not available.

[a]Homozygous and heterozygous carriers were grouped together; it is not possible to extract data for each state.

aspirin alone (RR, 0.78; 95% CI, 0.39-1.57).[252,284] Similar results were obtained when LMWH and aspirin was compared with IV γ-globulin (RR, 0.37; 95% CI, 0.12-1.16).[252,281]

A subsequent meta-analysis that combined data from randomized trials testing the efficacy of a combination of heparin (either UFH or LMWH) and aspirin vs aspirin alone in patients with APLAs and recurrent pregnancy loss[292] included an additional LMWH study published since the first systematic review.[293] When data from five trials (n = 334) were combined, the frequency of live births was significantly higher in the aspirin and heparin group (74.3%) than in those randomized to aspirin alone (55.8%) (RR, 1.3; 95% CI, 1.0-1.7; NNT to achieve one live birth, 5.6).[292] When studies that used LMWH and UFH were analyzed separately, there was just a trend of higher birth rate in patients receiving aspirin and LMWH (RR, 1.1; 95% CI, 0.9-1.3). Although the relative effectiveness of UFH vs LMWH with respect to prevention of recurrent pregnancy loss in women with APLAs is not established, the results of two small pilot studies (n = 26 and n = 50) suggest that the combination of LMWH and aspirin might at least be equivalent to UFH and aspirin in preventing recurrent pregnancy loss (RR, 0.44 [95% CI, 0.17-1.00][285] and 0.8 [95% CI, 0.26-2.48][286] in women receiving LMWH vs UFH, respectively). Given the absence of evidence that women with APLA syndrome and a single late pregnancy loss, preeclampsia, or fetal growth restriction benefit from the addition of UFH or LMWH to aspirin, we do not recommend for or against screening for APLAs in women with these pregnancy complications.

The data addressing the use of antithrombotic therapy in women with inherited thrombophilia and pregnancy loss consists of predominantly small uncontrolled trials or observational studies with important methodological limitations.[288,289,294-302] Gris et al[297] reported that enoxaparin in women with factor V Leiden, the prothrombin gene mutation, or protein S deficiency and one previous pregnancy loss increased the live birth rate (86%) compared with low-dose aspirin alone (29%); however, the methodology and results of this randomized trial have generated much controversy,[300,303-305] and we have not included it in the evidence we used to make recommendations. A subsequent cohort study found the live birth rate of subsequent pregnancies after a single pregnancy loss at or later than 12 weeks gestation in carriers of factor V Leiden or the prothrombin mutation was, without intervention, 68% (95% CI, 46%-85%).[306]

Tables S21 and S22 summarize the methodology and results of randomized trials and nonrandomized observational studies (excluding those that used a historical control group). These data do not provide

Table 10—*[Section 10.2.1,10.2.3] Summary of Findings: Should UFH Plus Aspirin or Aspirin Alone Be Used for Pregnant Women With APLA and Recurrent Pregnancy Loss*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects During Pregnancy: Risk With Aspirin	Anticipated Absolute Effects During Pregnancy: Risk Difference With UFH + Aspirin (95% CI)
Pregnancy loss	212 (3 RCTs), not reported	Moderate due to risk of bias[b]	RR 0.44 (0.33- 0.66)	500 losses per 1,000[a]	283 fewer losses per 1,000 (from 353 fewer to 172 fewer)
IUGR[c]	134 (3 RCTs), not reported	Low due to risk of bias[b] and imprecision[d]	RR 1.71 (0.48-6.17)	56 IUGR per 1,000[a]	No significant difference; 39 more IUGR per 1,000 (from 29 fewer to 287 more)
Preeclampsia not clearly defined	134 (3 RCTs), not reported	Low due to risk of bias[b] and imprecision[d]	RR 0.43 (0.09-2.08)	74 cases per 1,000[a]	No significant difference; 30 fewer cases per 1,000 (from 67 fewer to 80 more)

Data from unpublished meta-analysis based on three trials.[278,279,290] Major bleeding is a critical outcome that was not reported in the three trials. APLA = antiphospholipid antibody; IUGR = intrauterine growth restriction; UFH = unfractionated heparin. See Table 2 legend for expansion of other abbreviations.

[a]Control group risk estimates with aspirin come from the meta-analysis of three trials.

[b]Risk of bias due to issues of randomization, allocation concealment, and blinding.

[c]Estimated fetal weight below the 10th percentile for gestational age.

[d]Wide CIs include benefit and harm.

evidence that LMWH improves pregnancy outcome in women with inherited thrombophilia and recurrent pregnancy loss.

Recommendations

10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for APLAs (Grade 1B)**.**

10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C)**.**

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B)**.**

10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C)**.**

11.0 Management of Women With a History of Preeclampsia or Recurrent Fetal Loss and No Thrombophilia

Preeclampsia is associated with microvascular fibrin deposition indicative of activation of platelets and coagulation[307] as well as widespread endothelial dysfunction.[308-310] The manifestations of this disease are protean,[310] and preeclampsia should not be considered as a single disease entity but rather as a maternal response to abnormal placentation.[311,312] Women with a thrombophilic disorder, whether it be acquired or heritable, may be more likely to develop preeclampsia, but for heritable thrombophilias, this association is largely based on retrospective case-control (Table 9) and cohort studies[151]; prospective investigations have not confirmed these findings.[275,313]

11.1 Prevention of Recurrent Preeclampsia in Women With No Thrombophilia

The observations of endothelial dysfunction and platelet dysfunction in preeclampsia led to the hypothesis that antiplatelet agents might prevent or delay the development of this condition. Systematic review results suggest that the use of antiplatelet agents (primarily low-dose aspirin) is associated with modest reductions in the relative risk of preeclampsia. Table 11[314,315] and Table S24 summarize the evidence and main findings from the most recent Cochrane review of 43 randomized trials with 32,590 women,[314] providing moderate-quality evidence of a significant reduction (RR, 0.83; 95% CI, 0.77-0.89) in the risk of preeclampsia associated with the use of antiplatelet agents. The relative effect of antiplatelet therapy appears to be similar in women at low and high risk for preeclampsia (ie, no evidence of subgroup effect). However, as shown in Table 11 and Table S24, the baseline risk of preeclampsia determines the absolute effect of antiplatelet therapy, and women at low risk have a substantially lower benefit (NNT, 100) than

Table 11—*[11.1.1] Summary of Findings: Should Aspirin Rather Than No Treatment Be Used for Prevention of Preeclampsia in Women Without Thrombophilia*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects During Pregnancy	
				Risk Without Antiplatelet Therapy	Risk Difference With Antiplatelet Therapy (95% CI)
Preeclampsia defined as proteinuric preeclampsia in Cochrane Systematic Review	32,590 (43 RCTs), not reported	Moderate due to inconsistency[b]	RR 0.83 (0.77-0.89)	Low risk for preeclampsia[c] 60 cases per 1,000[a]	10 fewer cases per 1,000 (from 14 fewer to 7 fewer)
				High risk for preeclampsia[c] 210 cases per 1,000[a]	36 fewer losses per 1,000 (from 46 fewer to 23 fewer)
Major bleeding events[d]	95,000 (6 RCTs), 3.8-10 y	Moderate due to indirectness[e]	RR 1.54 (1.30-1.82)	15 bleeding events per 1,000[f]	8 more bleeding events per 1,000 (from 5 more to 12 more)

Data from Duley et al[314] and ATT Collaboration.[315] See Table 2 legend for expansion of abbreviations.

[a]Control group risk estimates for preeclampsia is based on control event rates in studies included in subgroup analyses in the meta-analysis.

[b]Heterogeneity ($I^2 = 46\%$, $P < .001$) might be related to different types and doses of antiplatelet agents, the lack of placebo in the control group in many of the trials, different populations of pregnant women concerning risk of preeclampsia, and effect of treatment.

[c]High risk was defined in the systematic review: Women who were either normotensive or had chronic hypertension without superimposed preeclampsia at trial entry were classified as being at high risk if they had one or more of the following: previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease. Low risk constitutes women without these characteristics.

[d]Major antenatal nonfatal hemorrhage.

[e]Rated down for indirectness due to population (primary prevention cardiovascular disease).[315] The Cochrane Review does not report the effects of antiplatelet therapy on major bleeding events in pregnant women.

[f]Control group risk estimate for major bleeding events antepartum from systematic review by Greer et al.[38]

women at high risk (NNT, 28). Current data from the Cochrane review do not show a difference in effect when low-dose aspirin is started before or after 20 weeks gestation.[314]

What constitutes high risk for preeclampsia is not always immediately clear, as available studies have used different risk stratification schemes. In identifying levels of risk, studies quantifying the risk of preeclampsia[312,316,317] suggested a relative risk of more than sevenfold with APLAs and previous preeclampsia and an approximately twofold increase in relative risk associated with a BMI ≥ 35 kg/m^2, preexisting diabetes, twin pregnancy, and a family history of preeclampsia. According to the Cochrane systematic review, women who were either normotensive or had chronic hypertension without superimposed preeclampsia at trial entry were classified as being at high risk if they had one or more of the following: previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease.[314]

Some have suggested anticoagulant therapy with LMWH or UFH for women at very high risk for preeclampsia. An effect of anticoagulant therapy on the risk of preeclampsia is biologically plausible not only because of a reduction in thrombosis formation but also because LMWH has been shown to have an antiapoptotic effect on trophoblasts,[248,318] a potential trigger for preeclampsia. However, an observational study of 58 women with previous preeclampsia and an underlying thrombophilia found no difference in the risk of preeclampsia between those treated with LMWH and low-dose aspirin vs those treated with low-dose aspirin alone or no prophylactic therapy.[319] In a randomized trial of 80 nonthrombophilic women considered to be at increased risk for preeclampsia on the basis of both a history and an underlying angiotensin-converting enzyme insertion/deletion polymorphism that examined the effect of prophylactic LMWH (dalteparin 5,000 units/d) on the pregnancy outcome, maternal BP, and uteroplacental flow,[320] women receiving LMWH had a lower incidence of adverse outcomes, with a 74.1% reduction in preeclampsia (RR, 0.26; 95% CI, 0.08-0.86) and a 77.5% reduction in fetal growth restriction (RR, 0.14; 95% CI, 0.03-0.56). A subsequent pilot study of 116 pregnant women with no detectable thrombophilia and previous severe preeclampsia, small for gestational age baby, placental abruption, or intrauterine fetal demise randomized to prophylactic-dose dalteparin or no dalteparin reported that dalteparin was associated with a lower rate of a composite of one or more of severe preeclampsia, birth weight in the fifth percentile or less, or major abruption (adjusted OR, 0.15; 95% CI, 0.03-0.70).[321]

The results of these studies need to be interpreted with some caution. First, it is not clear whether the positive effects of LMWH on prevention of preeclampsia in women with underlying angiotensin-converting enzyme insertion/deletion polymorphisms are broadly generalizable. Second, the pilot study

was stopped before reaching its planned sample size of 276 when an interim analysis performed because of slow accrual suggested a statistically significant decrease in the primary outcome, potentially exaggerating the treatment effect.[322,323]

Recommendation

11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B)**.**

11.2 Women Without Known Thrombophilia and at Least Two Prior Pregnancy Losses

A Cochrane systematic review from 2009 that examined the use of aspirin and anticoagulation for recurrent pregnancy loss in women without APLA syndrome[324] identified two randomized trials: one comparing aspirin to placebo (n = 54)[283] and the other comparing enoxaparin to aspirin (n = 107).[325] Neither of the studies found significant differences in live birth rates, which ranged from 81% to 84%. Another systematic review, published in 2010, of LMWH vs aspirin or LMWH vs no treatment/placebo identified five randomized trials (n = 757).[326] The studies reviewed varied in terms of definition of early or late pregnancy loss, thrombophilic risk factors, and number of prior pregnancy losses. No meta-analysis was performed in the systematic review due to clinical heterogeneity of the studies. Risk ratios for pregnancy loss in the individual studies ranged from 0.95 to 3.0. The authors of this systematic review concluded that there was low-quality evidence, suggesting no effect of LMWH or aspirin. Two randomized trials have subsequently been published that provide relevant evidence on the effects of LMWH plus aspirin vs aspirin or placebo/no treatment on recurrent idiopathic pregnancy loss.[327,328]

11.2.1 LMWH and Aspirin vs No Treatment or Placebo: Table 12 and Table S25 summarize the quality of evidence and main findings from our meta-analysis of the two randomized trials that included 538 women with at least two miscarriages.[327,328] The meta-analysis provides moderate-quality evidence that LMWH and aspirin do not reduce miscarriage or increase major bleeding events in women with at least two recurrent miscarriages.

Women with three or more pregnancy losses might benefit from anticoagulant therapy. Two randomized trials of women with three or more pregnancy losses reported a substantial benefit of LMWH therapy on miscarriages.[329,330] However, both of these studies had important methodologic limitations, including a lack of blinding[329] or uncertain blinding,[330] relatively high rates of loss to follow-up,[329,330] lack of prospective trial registration,[329,330] and an unexpectedly low live birth rate in the placebo arm.[330] These findings are challenged by findings from the more recent high-quality randomized trials described previously in the present article. In one of these studies, a prespecified subgroup analysis of women with three or more miscarriages showed no evidence of a different relative effect of LMWH and aspirin vs placebo (test for interaction $P = .85$).[327] The other study provided data for the same subgroup of women and found no difference in effect (27% miscarriages in treatment group vs 24% in control group), although no formal subgroup analysis was performed.[326] We consider these findings more credible than those of the two lower-quality randomized

Table 12—*[Section 11.2.1] Summary of Findings: Should LMWH and Aspirin Rather Than No Treatment Be Used for Prevention of Recurrent Pregnancy Loss in Women Without Thrombophilia*

				Anticipated Absolute Effects During Pregnancy	
Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Risk Without Treatment	Risk Difference With LMWH + Aspirin (95% CI)
Miscarriage	496 (2 RCTs), 9 mo	Moderate due to imprecision[b]	RR 1.01 (0.84-1.38)	300 cases of miscarriage per 1,000[c]	No significant difference; 3 more cases per 1,000 (from 48 fewer to 114 more)
Major bleeding events[d]	294 (1 RCTs), 9 mo	Moderate due to imprecision[b]	RR 1.00 (0.42-2.33)	15 bleeding events per 1,000[e]	No significant difference; 0 more bleeding events per 1,000 (from 9 fewer to 20 more)

Data from unpublished meta-analysis[1] of two RCTs by Kaandorp et al[327] and Clark et al.[328] See Table 2 for expansion of abbreviations.

[a]Wide CIs include benefit and harm.

[b]Meta-analysis performed in RevMan version 5 with fixed-effects model for heterogeneity.

[c]Control group risk for miscarriage comes from study event rates in the two available randomized trials.[327,328]

[d]Antepartum maternal major hemorrhage. Bleeding outcomes variably reported in the two trials. We use data from Clark et al[328] on serious adverse events and antepartum hemorrhage both to generate relative risks and baseline risks for anticipated absolute effects. Kaandorp et al[327] reported nosebleed, GI problems, hematuria, and bleeding gums. There were no major bleeding events (S. Middeldorp, MD, personal communication, October 2010).

[e]Control group risk estimate for major bleeding events antepartum with aspirin comes from systematic review by Greer et al.[38]

trials; however, a possible deleterious effect of aspirin on pregnancy outcome when used in combination with LMWH cannot be excluded.

11.2.2 Aspirin vs Placebo: Table 13 and Table S26 summarize the main findings from a randomized comparison of 104 women allocated to aspirin and 103 women with two or more unexplained recurrent miscarriages allocated to placebo.[327] This trial provides moderate-quality evidence that aspirin does not improve live birth rates among women with two or more unexplained recurrent miscarriages. Similarly, the randomized trial of low-dose aspirin vs placebo[283] that included 54 women with three or more pregnancy losses did not find a significant difference in miscarriages (RR, 1.00; 95% CI, 0.78-1.29).

Recommendation

11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B)**.**

12.0 Maternal and Fetal Risks Related to Anticoagulation During Pregnancy for Mechanical Prosthetic Valves

Patients with a mechanical heart valve not receiving antithrombotic therapy face a high risk of valve thrombosis and death or systemic embolism (see Whitlock et al[331] in this guideline). However, as outlined in section 3.0, the use of vitamin K antagonists during pregnancy carries potential for risks to the fetus, especially if these drugs are administered during the first trimester or at term. Although LMWH or UFH can be substituted for vitamin K antagonists, doubt has been raised about their effectiveness for prevention of systemic embolism in this setting. Unfortunately, properly designed trials have not been performed, and even the small amount of data available is limited by significant heterogeneity for valve type; valve position; valve area; and presence of comorbid conditions, such as atrial fibrillation.

12.1 Anticoagulant Management of Mechanical Prosthetic Valves in Pregnant Women

Tables S27 and S28 present the available data regarding maternal outcomes in this setting.[49,50,332-340] In a systematic review of observational studies between 1966 and 1997 that reported on outcomes with various anticoagulant regimens in pregnant women with mechanical prosthetic valves, the regimen associated with the lowest risk of valve thrombosis/systemic embolism was the use of vitamin K antagonists throughout pregnancy (3.9%).[49] The use of UFH in the first trimester and near term was associated with a higher risk of valve thrombosis (9.2%).[49] The risk of thromboembolic complications was highest when UFH was used throughout pregnancy (33.3%),[49] and events occurred in women receiving both IV and adjusted-dose subcutaneous UFH and in those treated with low-dose heparin. Although these data suggest that vitamin K antagonists are more effective than UFH for thromboembolic prophylaxis of pregnant women with mechanical heart valves, some of the thromboembolic events in women treated with UFH might be explained by inadequate dosing, use of an inappropriate target aPTT range, or differences in risk profile in the patient populations treated with UFH vs those treated with vitamin K antagonists.

LMWH has advantages over UFH in terms of the maternal side effect profile, and there is increasing use of LMWH in pregnant women with prosthetic heart

Table 13—*[Section 11.2.1] Summary of Findings: Should Aspirin Rather Than No Treatment Be Used for Prevention of Recurrent Pregnancy Loss in Women Without Thrombophilia*

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[a]	Anticipated Absolute Effects During Pregnancy: Risk Without Aspirin	Anticipated Absolute Effects During Pregnancy: Risk Difference With Aspirin (95% CI)
Miscarriage	202 (1 RCT), 9 mo	Moderate due to imprecision[a]	RR 1.16 (0.80-1.69)	300 cases of miscarriage per 1,000[b]	No significant difference; 48 more cases per 1,000 (from 60 fewer to 207 more)
Major bleeding events[c]	95 000 (6), 3.8-10 y	Moderate due to indirectness[d]	RR 1.54 (1.30-1.82)	15 bleeding events per 1,000[e]	8 more bleeding events per 1,000 (from 5 more to 12 more)

Data from Kaandorp et al,[327] the only study identified that compared aspirin to placebo in this population, and ATT Collaboration,[315] for relative effect estimate of major bleeding events. See Table 2 legend for expansion of abbreviations.

[a]Wide CIs include benefit and harm of aspirin on miscarriage.

[b]Baseline risk for miscarriage comes from study event rates in the two available randomized trials.[327,328]

[c]Major antenatal nonfatal hemorrhage.

[d]Rated down for indirectness due to population (primary prevention cardiovascular disease).[315] There were no major bleeding events in the Anticoagulants for LIving Fetuses (ALIFE) Study[327] (S. Middeldorp, MD, personal communication, October 2010).

[e]Control group risk estimate for major bleeding events antepartum comes from systematic review by Greer et al.[38]

valves. The safety of LMWH for this indication was questioned in a warning from an LMWH manufacturer.[341] This warning was based on postmarketing reports of valve thrombosis in an undisclosed number of patients receiving this LMWH as well as on clinical outcomes in an open randomized study comparing LMWH (enoxaparin) with warfarin and UFH in pregnant women with prosthetic heart valves.[341] Because of two deaths in the LMWH arm, the study was terminated after 12 of the planned 110 patients were enrolled.

In a systematic review of observational studies published between 2000 and 2009, the use of LMWH (or UFH) during the first trimester and near term or throughout pregnancy was associated with a higher risk of valve thrombosis or maternal thromboembolism (7.2% and 13.4%, respectively) than the use of vitamin K antagonists alone (2.9%).[50] Maternal bleeding risks were similar across the various treatment regimens.

In a review of case series and cohort studies between 1996 and 2006 involving pregnant women with mechanical heart valves who were converted to LMWH prior to pregnancy or by the end of the first trimester, maternal valve thrombosis or thromboembolism occurred in 17 of 76 (22.4%) pregnancies.[332] Another systematic review of LMWH use in pregnant women with mechanical prosthetic heart valves that used slightly different eligibility criteria found that valve thrombosis occurred in seven of 81 pregnancies (8.6%; 95% CI, 2.5%-14.8%), and the overall thromboembolic rate was 10 of 81 pregnancies (12.4%; 95% CI, 5.2%-19.5%).[333] However, nine of the 10 patients with thromboembolic complications received a fixed dose of LMWH, and in two of these, a fixed low dose was used. Among 51 pregnancies in which anti-Xa LMWH levels were monitored and doses adjusted according to the result, only one patient was reported to have experienced a thromboembolic complication. Two subsequent case series[334,335] and one cohort study without internal control[336] that evaluated LMWH given every 12 h and adjusted to maintain therapeutic peak anti-Xa LMWH levels reported risks of maternal valve thrombosis or systemic thromboembolism ranging between 4.3% and 16.7%.

As outlined in Table S29, the use of UFH or LMWH throughout pregnancy essentially eliminates the risk of congenital malformation.[49,50,332-336] Most published studies suggest that risks of malformation are also low (< 2%) if UFH or LMWH are substituted for vitamin K antagonists during the first trimester (preferably before the 6th week of gestation).[49,50,332-336] The number of pregnancy losses appears higher in those patients who receive either vitamin K antagonists or a heparin throughout pregnancy than in those in whom UFH or LMWH are substituted for vitamin K antagonists in the first trimester and at term.[49,50,332-340]

Thus, it appears that there is no single optimal treatment approach for managing pregnant women with mechanical prosthetic valves. Given the limited and sometimes conflicting data, several approaches remain acceptable (Table 14). The decision about which regimen to use should be made after full discussion with the patient. Additional risk factors for thromboembolism as well as patient preference should be taken into consideration. For example, women at very high risk (eg, first-generation mechanical valve in the mitral position, history of thromboembolism, associated atrial fibrillation) may prefer vitamin K antagonist use throughout pregnancy. If warfarin is used, the dose should be adjusted as recommended by Whitlock et al.[331] If subcutaneous UFH is used, it should be initiated in high doses (17,500-20,000 units every 12 h) and adjusted to prolong a 6-h postinjection aPTT into the therapeutic range. If LMWH is used, it should be administered bid and dosed to achieve the manufacturer's peak anti-Xa level 4 h after subcutaneous injection. Extrapolating from data in nonpregnant patients with mechanical valves receiving warfarin therapy,[342] for the same high-risk women, the addition of aspirin 75 to 100 mg/d can be considered in an attempt to reduce the risk of thrombosis, recognizing that it increases the risk of bleeding.

Recommendations

12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A)**:**

(a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted

Table 14—*[12.1.1-12.1.3] Recommended Anticoagulant Regimens in Pregnant Women With Mechanical Heart Valves*

Adjusted-dose bid LMWH throughout pregnancy, with doses adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous injection (Grade 1A).
Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the midinterval aPTT at least twice control or attain an anti-Xa heparin level of 0.35-0.70 units/mL (Grade 1A).
UFH or LMWH (as above) until the 13th week with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed (Grade 1A).
For women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older-generation prosthesis in the mitral position or history of thromboembolism), vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery (Grade 2C).

aPTT = activated partial thromboplastin time. See Table 2 and 10 legends for expansion of abbreviations.

to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous injection; or
(b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the midinterval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL; or
(c) UFH or LMWH (as above) until the 13th week with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed.

Remarks: For pregnant women with mechanical heart valves, the decision regarding the choice of anticoagulant regimen is so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that we consider the decision to be completely individualized. Women of childbearing age and pregnant women with mechanical valves should be counseled about potential maternal and fetal risks associated with various anticoagulant regimens, including continuation of vitamin K antagonists with substitution by LMWH or UFH close to term, substitution of vitamin K antagonists by LMWH or UFH until the 13th week and then close to term, and use of LMWH or UFH throughout pregnancy. Usual long-term anticoagulants should be resumed postpartum when adequate hemostasis is assured.

12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older-generation prosthesis in the mitral position or history of thromboembolism), we suggest vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C)**.**

Remarks: The recommendation for women at very high risk of thromboembolism places a higher value on avoiding maternal complications (eg, catastrophic valve thrombosis) than on avoiding fetal complications. Women who place a higher risk on avoiding fetal risk will choose LMWH or UFH over vitamin K antagonists.

12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin 75 to 100 mg/d (Grade 2C)**.**

13.0 Recommendations for Research

Although new information has been published since our last review, the available evidence in this article is still generally of low quality. Most recommendations are based on observational studies and extrapolation from other populations. There is an urgent need for appropriately designed studies to inform us of the risk of recurrent pregnancy-associated VTE and of first VTE in thrombophilic women and those undergoing cesarean section and assisted reproductive technology. Further research is needed to optimize regimens for the prevention of VTE and mechanical valve thrombosis. Given the uncertainty of baseline estimates for both the risks of the various conditions discussed in this article and the benefits of prophylactic and therapeutic interventions, knowledge of pregnant women's values and treatment preferences are crucial when making recommendations. Although investigators have explored patient values and preferences with respect to antithrombotic therapy in other contexts, no studies have been performed in pregnant women.

Although the performance of clinical trials involving pregnant women is challenging, there is a clear need for methodologically strong studies in this patient population. All pregnant women are best protected when evidence about conditions that affect them is gathered in a scientifically rigorous manner that maximizes participant safety.[343]

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Dr Greer: contributed as a panelist.
Dr Middeldorp: contributed as a panelist.
Dr Veenstra: contributed as a resource consultant.
Dr. Prabulos: contributed as a front line clinician.
Dr Vandvik: contributed as Topic Editor.
Financial/nonfinancial disclosures: The authors of this guideline provided detailed conflict of interest information related to each individual recommendation made in this article. A grid of these disclosures is available online at http://chestjournal.chestpubs.org/content/141/2_suppl/e691S/suppl/DC1. In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Bates has received honoraria for lectures from Leo Pharma, Inc. (anticoagulant manufacturer), Sanofi-Aventis Canada (anticoagulant manufacturer), Boehringer Ingelheim GmbH (anticoagulant manufacturer), and Thrombosis Education, Ltd. Dr Greer has received honoraria for lectures and advisory board contributions from Leo Pharma and Sanofi-Aventis. Dr Middeldorp has received unrestricted research funding from GlaxoSmithKline plc and MedaPharma for the ALIFE study and has received speakers fees from GlaxoSmithKline plc; Boehringer Ingelheim GmbH; Bayer Healthcare Pharmaceuticals; Leo Pharma, Inc. Dr Vandvik is a member of and prominent contributor to the GRADE Working Group. Drs Veenstra and Prabulos have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
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Additional Information: The supplement Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e691S/suppl/DC1.

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