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Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy, and Pregnancy*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article discusses the management of venous thromboembolism (VTE) and thrombophilia, as well as the use of antithrombotic agents, during pregnancy and is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that benefits do, or do not, outweigh risks, burden, and costs. Grade 2 recommendations are weaker and imply that the magnitude of the benefits and risks, burden, and costs are less certain. Support for recommendations may come from high-quality, moderate-quality or low-quality studies; labeled, respectively, A, B, and C.

Among the key recommendations in this chapter are the following: for pregnant women, in general, we recommend that vitamin K antagonists should be substituted with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) [Grade 1A], except perhaps in women with mechanical heart valves. For pregnant patients, we suggest LMWH over UFH for the prevention and treatment of VTE (Grade 2C). For pregnant women with acute VTE, we recommend that subcutaneous LMWH or UFH should be continued throughout pregnancy (Grade 1B) and suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months) [Grade 2C].

For pregnant patients with a single prior episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, we recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum (Grade 1C). For other pregnant women with a history of a single prior episode of VTE who are not receiving long-term anticoagulant therapy, we recommend one of the following, rather than routine care or full-dose anticoagulation: antepartum prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants (Grade 1C). For such patients with a higher risk thrombophilia, in addition to postpartum prophylaxis, we suggest antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH, rather than clinical surveillance (Grade 2C). We suggest that pregnant women with multiple episodes of VTE who are not receiving long-term anticoagulants receive antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH or intermediate or adjusted-dose UFH, followed by postpartum anticoagulants (Grade 2C). For those pregnant women with prior VTE who are receiving long-term anticoagulants, we recommend LMWH or UFH throughout pregnancy (either adjusted-dose LMWH or UFH, 75% of adjusted-dose LMWH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum (Grade 1C).

We suggest both antepartum and postpartum prophylaxis for pregnant women with no prior history of VTE but antithrombin deficiency (Grade 2C). For all other pregnant women with thrombophilia but no prior VTE, we suggest antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants, rather than routine care (Grade 2C).

For women with recurrent early pregnancy loss or unexplained late pregnancy loss, we recommend screening for antiphospholipid antibodies (APLAs) [Grade 1A]. For women with these pregnancy complications who test positive for APLAs and have no history of venous or arterial thrombosis, we recommend antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin (Grade 1B).

We recommend that the decision about anticoagulant management during pregnancy for pregnant women with mechanical heart valves include an assessment of additional risk factors for thromboembolism including valve type, position, and history of thromboembolism (Grade 1C). While patient values and preferences are important for all decisions regarding antithrombotic therapy in pregnancy, this is particularly so for women with mechanical heart valves. For these women, we recommend either adjusted-dose bid LMWH throughout pregnancy (Grade 1C), adjusted-dose UFH throughout pregnancy (Grade 1C), or one of these two regimens until the thirteenth week with warfarin substitution until close to delivery before restarting LMWH or UFH) [Grade 1C]. However, if a pregnant woman with a mechanical heart valve is judged to be at very high risk of thromboembolism and there are concerns about the efficacy and safety of LMWH or UFH as dosed above, we suggest vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH close to delivery, after a thorough discussion of the potential risks and benefits of this approach (Grade 2C).

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Key words: anticoagulation; breast feeding; deep vein thrombosis; heparin; low-molecular-weight heparin; mechanical heart valves; pregnancy; prophylaxis; pulmonary embolism; venous thromboembolism; thrombophilia; treatment; warfarin

Abbreviations: APLA = antiphospholipid antibody; aPTT = activated partial thromboplastin time; CI = confidence interval; DVT = deep vein thrombosis; HELLP = hemolysis, elevated liver enzymes, and low platelets syndrome; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IUGR = intrauterine growth restriction; LMWH = low-molecular-weight heparin; MRV = MRI venography; OR = odds ratio; PE = pulmonary embolism; RR = relative risk; UFH = unfractionated heparin; VTE = venous thromboembolism

Summary of Recommendations

When describing the various regimens of UFH and LMWH, we will use the following short forms:
–Prophylactic UFH: UFH 5,000 U subcutaneously q12h.
–Intermediate-dose UFH: UFH subcutaneously q12h in doses adjusted to target an anti-Xa level of 0.1 to 0.3 U/mL.
–Adjusted-dose UFH: UFH subcutaneously q12h in doses adjusted to target a mid-interval activated partial thromboplastin time (aPTT) into the therapeutic range.
–Prophylactic LMWH: *eg*, dalteparin 5,000 U subcutaneously q24h, tinzaparin 4,500 U subcutaneously q24h, or enoxaparin 40 mg subcutaneously q24h (although at extremes of body weight modification of dose may be required).
–Intermediate-dose LMWH: *eg*, dalteparin 5,000 U subcutaneously q12h or enoxaparin 40 mg subcutaneously q12h.
–Adjusted-dose LMWH: weight-adjusted, full treatment doses of LMWH, given once or twice daily (*eg*, dalteparin 200 U/kg or tinzaparin 175 U/kg qd or dalteparin 100 U/kg q12h or enoxaparin 1 mg/kg q12h).
–Postpartum anticoagulants: vitamin K antagonists for 4 to 6 weeks with a target INR of 2.0 to 3.0, with initial UFH or LMWH overlap until the INR is ≥ 2.0, or prophylactic LMWH for 4 to 6 weeks.
–In addition, the term *surveillance* refers to clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis (DVT) or pulmonary embolism (PE).

2.1 Vitamin K Antagonist Exposure In Utero

2.1.1. For women receiving anticoagulation for the management of VTE who become pregnant, we recommend that vitamin K antagonists be substituted with UFH or LMWH (Grade 1A)**.**
2.1.2. For women with mechanical valves who become pregnant, we suggest either adjusted-dose bid LMWH or UFH throughout pregnancy or adjusted-dose bid LMWH or UFH until the thirteenth week with substitution by vitamin K antagonists until LMWH or UFH are resumed close to delivery (Grade 1C)**. In pregnant women with high-risk mechanical valves (*eg*, older generation valve in the mitral position or history of thromboembolism), we suggest the use of oral anticoagulants over heparin** (Grade 2C)**.**
Underlying values and preferences: The suggestion to utilize vitamin K antagonists during the first 12 weeks of pregnancy places similar value on avoiding maternal thromboembolic complications as on avoiding fetal risks.

2.2 Management of Women Receiving Long-term Vitamin K Antagonists Who Are Considering Pregnancy

2.2.1. For women requiring long-term vitamin K antagonists who are attempting pregnancy and are candidates for UFH or LMWH substitution, we suggest performing frequent pregnancy tests and substituting UFH or LMWH for vitamin K antagonists when pregnancy is achieved (Grade 2C)**.**
Underlying values and preferences: This recommendation places a higher value on avoiding the risks, inconvenience, and costs of UFH or LMWH therapy of uncertain duration while awaiting pregnancy compared to minimizing the risks of early miscarriage associated with vitamin K antagonist therapy.

3.0 Use of Anticoagulants in Nursing Women

3.0.1. For lactating women using warfarin or UFH who wish to breastfeed, we recommend continuing these medications (Grade 1A)**.**
3.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, we suggest continuing these medications (Grade 2C)**.**
3.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than pentasaccharides (Grade 2C)**.**

4.2 LMWH Therapy

4.2.1. For pregnant patients, we suggest LMWH over UFH for the prevention and treatment of VTE (Grade 2C)**.**

5.1 Risk of VTE Following Cesarean Section

5.1.1. We suggest that a thrombosis risk assessment be carried out in all women undergoing

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cesarean section to determine the need for thromboprophylaxis (Grade 2C).

5.1.2. In patients without additional thrombosis risk factors undergoing cesarean section, we recommend against the use of specific thromboprophylaxis other than early mobilization (Grade 1B).

5.2 Thromboprophylaxis Following Cesarean Section

5.2.1. For women considered at increased risk of VTE after cesarean section because of the presence of at least one risk factor in addition to pregnancy and cesarean section, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH or UFH) or mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression) while in hospital following delivery (Grade 2C).

5.2.2. For women with multiple additional risk factors for thromboembolism who are undergoing cesarean section and are considered to be at very high risk of VTE, we suggest that pharmacologic prophylaxis be combined with the use of graduated compression stockings and/or intermittent pneumatic compression (Grade 2C).

5.2.3. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 4 to 6 after delivery) following discharge from the hospital (Grade 2C).

6.1 Treatment of VTE During Pregnancy

6.1.1. For pregnant women with acute VTE, we recommend initial therapy with either adjusted-dose subcutaneous LMWH or adjusted-dose UFH (IV bolus, followed by a continuous infusion to maintain the aPTT within the therapeutic range or subcutaneous therapy adjusted to maintain the aPTT 6 h after injection into the therapeutic aPTT range) for at least 5 days (Grade 1A).

6.1.2. For pregnant women with acute VTE, after initial therapy, we recommend that subcutaneous LMWH or UFH should be continued throughout pregnancy (Grade 1B).

6.1.3. 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 6 months) [Grade 2C].

6.1.4. For pregnant women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuation of the heparin at least 24 h prior to elective induction of labor (Grade 1C).

7.2 Prevention of Recurrent VTE in Pregnant Women

7.2.1. For pregnant women with a single episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, we recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum (Grade 1C).

7.2.2. If the transient risk factor associated with a previous VTE event is pregnancy or estrogen related, we suggest antepartum clinical surveillance or prophylaxis (prophylactic LMWH/UFH or intermediate-dose LMWH/UFH) plus postpartum prophylaxis, rather than routine care (Grade 2C).

7.2.3. For pregnant women with a single idiopathic episode of VTE but without thrombophilia and who are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants (Grade 1C).

7.2.4. For pregnant women with thrombophilia (confirmed laboratory abnormality) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH or clinical surveillance throughout pregnancy; plus post-partum anticoagulants (Grade 1C).

7.2.5. For women with "higher risk" thrombophilias (*eg*, antithrombin deficiency, persistent positivity for the presence of antiphospholipid antibodies; compound heterozygosity for prothrombin G20210A variant and factor V Leiden or homozygosity for these conditions) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, we suggest, in addition to postpartum prophylaxis, antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH, rather than clinical surveillance (Grade 2C).

7.2.6. For pregnant women with multiple (≥ 2) episodes of VTE not receiving long-term anticoagulants, we suggest antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH or prophylactic, intermediate or adjusted-dose UFH followed by postpartum anticoagulants rather than clinical surveillance (Grade 2C).

7.2.7. For pregnant women receiving long-term anticoagulants for prior VTE, we recom-

mend LMWH or UFH throughout pregnancy (either adjusted-dose LMWH or UFH, 75% of adjusted-dose LMWH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum (Grade 1C).

7.2.8. For all pregnant women with previous DVT, we suggest the use of graduated elastic compression stockings both antepartum and postpartum (Grade 2C).

Underlying values and preferences: This recommendation places a high value on uncertain incremental benefit with stockings, and a low value on avoiding discomfort and inconvenience.

8.1 Risk of Pregnancy-Related VTE in Women With Thrombophilia

8.1.1. For pregnant patients with thrombophilia but no prior VTE, we recommend that physicians do not use routine pharmacologic antepartum prophylaxis but instead perform an individualized risk assessment (Grade 1C).

8.2 Prevention of Pregnancy-Related VTE in Women With Thrombophilia

8.2.1. For pregnant women with no history of VTE but antithrombin deficiency, we suggest antepartum and postpartum prophylaxis (Grade 2C).

8.2.2. For all other pregnant women with thrombophilia and no prior VTE, we suggest antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants (Grade 2C).

9.1 Risk of Pregnancy Complications in Women With Thrombophilia

9.1.1. For women with recurrent early pregnancy loss (three or more miscarriages) or unexplained late pregnancy loss, we recommend screening for APLAs (Grade 1A).

9.1.2. For women with severe or recurrent preeclampsia or IUGR, we suggest screening for APLAs (Grade 2C).

9.2 Prevention of Pregnancy Complications in Women With Thrombophilia

9.2.1. For women with APLAs and recurrent (three or more) pregnancy loss or late pregnancy loss and no history of venous or arterial thrombosis, we recommend antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin (Grade 1B).

10.1 Prevention of Recurrent Pre-eclampsia in Women With No Thrombophilia

10.1.1. For women considered high risk for preeclampsia, we recommend low-dose aspirin therapy throughout pregnancy (Grade 1B).

10.1.2. For women with a history of preeclampsia, we suggest that UFH and LMWH should not be used as prophylaxis in subsequent pregnancies (Grade 2C).

11.1 Anticoagulant Management of Mechanical Prosthetic Valves in Pregnant Women

11.1.1. For pregnant women with mechanical heart valves, we recommend that the decision about anticoagulant management during pregnancy include an assessment of additional risk factors for thromboembolism including valve type, position, and history of thromboembolism, and that the decision should also be influenced strongly by patient preferences (Grade 1C).

11.1.2. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation:

(a) adjusted-dose bid LMWH throughout pregnancy (Grade 1C)**. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h after subcutaneous injection,** (Grade 2C) **or**

(b) adjusted-dose UFH throughout pregnancy administered subcutaneously q12h 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 U/mL (Grade 1C)**, or**

(c) UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed (Grade 1C).

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, after a thorough discussion of the potential risks and benefits of this approach (Grade 2C).

Underlying values and preferences: In contrast to our other recommendations, which place a high value on avoiding fetal risk, the recommendation for women at very high risk of thromboembolism places equal value on avoiding maternal complications.

Remark: For all the recommendations above, usual long-term anticoagulants should be resumed postpartum.

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

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of venous thromboembolism (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. The use of anticoagulant therapy during pregnancy is challenging because of the potential for fetal, as well as maternal, complications. Given the paucity of data regarding the efficacy of anticoagulants during pregnancy, recommendations about their use in pregnant women are based largely on extrapolations from data from nonpregnant patients, from case reports, and from case series of pregnant patients.

Since our last review, investigators have published new information concerning the risk of VTE in pregnant women with thrombophilia, management of pregnant women with prior VTE, the treatment of VTE in pregnancy, the safety of low-molecular-weight heparin (LMWH) during pregnancy, the difficulties of managing pregnant women with mechanical heart valves, as well as the relation between thrombophilia and pregnancy complications and the use of anticoagulant therapy in this setting. Unfortunately, the additional publications have not achieved a dramatic improvement in the quality of available evidence.

In this chapter, we will review the management of thrombophilia, thromboembolic complications, and anticoagulant therapy during pregnancy, with particular emphasis on important new studies. Table 1 describes the search and eligibility criteria for the studies considered in each section of the recommendations that follow. Recommendations are based on the revised American College of Chest Physicians grades of recommendation.[1]

1.0 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 special considerations are of particular importance. First, treatment decisions during pregnancy and nursing have implications not only for the health and life of the mother but for the health and life of the fetus. Second, many women prefer to see pregnancy as a normal part of a healthy 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 choices.

While we are unaware of any research specifically addressing women's preferences regarding antithrombotic therapy in pregnancy, anecdotal evidence suggests that many, though not all women, give higher priority to the impact of any treatment on the health of their unborn baby than to effects on themselves. For example, consider the decision regarding heparin, typically administered through injection, vs coumarin derivatives, administered orally, as antithrombotic therapy during pregnancy. Our recommendations reflect a belief that most women will place 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.

Recommendations in this chapter, 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, even some of the strong recommendations in this chapter 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 Fetal Complications of Anticoagulant Therapy During Pregnancy

The antithrombotics currently available for the prevention and treatment of venous and arterial thromboembolism include heparin and heparin-like compounds (unfractionated heparin [UFH], LMWH, pentasaccharides, and heparinoids), coumarin derivatives, direct thrombin inhibitors, and antiplatelet agents. When considering antithrom-

Table 1—*Question Definition and Eligibility Criteria

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
2.1	Fetuses/children	Coumarin exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay PT, INR in umbilical cord blood	RCT; observational study	Maternal comorbid condition associated with adverse fetal outcome
2.3	Fetuses/children	UFH exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay Heparin levels in umbilical cord blood	RCT; observational study	Maternal comorbid condition associated with adverse fetal outcome
2.4	Fetuses/children	LMWH exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay Heparin levels in umbilical cord blood	RCT; observational study	Maternal comorbid condition associated with adverse fetal outcome
2.5	Fetuses/children of women using aspirin during pregnancy	Aspirin exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay Patent ductus arteriosus	RCT; observational study	Maternal comorbid condition associated with adverse fetal outcomes
2.6	Fetuses/children	Danaparoid exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay Heparin levels in umbilical cord blood	RCT; observational study	Comorbid condition associated with adverse fetal outcomes
2.7	Fetuses/children	Direct thrombin inhibitor exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay PT, INR, or aPTT in umbilical cord blood	RCT; observational study	Comorbid condition associated with adverse fetal outcomes
2.8	Fetuses/children	Pentasaccharide exposure *in utero* compared to no exposure	Fetal hemorrhage Fetal loss Congenital malformation Developmental delay Heparin levels in umbilical cord blood	RCT; observational study	Comorbid condition associated with adverse fetal outcomes
2.9	Fetuses/children	Thrombolysis during pregnancy compared to no thrombolysis	Fetal hemorrhage Fetal loss Congenital malformation	RCT; observational study	Comorbid condition associated with adverse fetal outcome
3.0	Breastfed infants (of women receiving coumarin derivatives)	Coumarin exposure during breastfeeding compared to no exposure	Infant hemorrhage Coumarin levels, PT, or INR in breast milk Coumarin levels, PT, or INR in infant blood	RCT; observational study	Comorbid condition associated with adverse infant outcome
3.0	Breastfed infants (of women receiving UFH)	UFH exposure during breastfeeding compared to no exposure	Infant hemorrhage aPTT or heparin levels in breast milk aPTT or heparin levels in infant blood	RCT; observational study	Comorbid condition associated with adverse infant outcome
3.0	Breastfed infants (of women receiving LMWH)	LMWH exposure during breastfeeding compared to no exposure	Infant hemorrhage Heparin levels in breast milk Heparin levels in infant blood	RCT; observational study	Comorbid condition associated with adverse infant outcome
3.0	Breastfed infants (of women receiving danaparoid)	Danaparoid exposure during breastfeeding compared to no exposure	Infant hemorrhage Heparin levels in breast milk Heparin levels in infant blood	RCT; observational study	Comorbid condition associated with adverse infant outcomes

Table 1—*Continued*

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
3.0	Breastfed infants (of women receiving direct thrombin inhibitors)	Direct thrombin inhibitor exposure during breastfeeding compared to no exposure	Infant hemorrhage aPTT, PT, or INR in breast milk aPTT, PT, or INR in infant blood	RCT; observational study	Comorbid condition associated with adverse infant outcomes
3.0	Breastfed infants (of women receiving pentasaccharide therapy)	Pentasaccharide exposure during breastfeeding compared to no exposure	Infant hemorrhage Heparin levels in breast milk Heparin levels in infant blood	RCT; observational study	Comorbid condition associated with adverse fetal outcomes
4.1	Pregnant women	UFH therapy during pregnancy (compared to no UFH heparin)	Maternal bleeding (major) Maternal bleeding (minor) Maternal HIT Maternal heparin-associated osteoporosis	RCT; observational study	None
4.2	Pregnant women	LMWH therapy during pregnancy (compared to no LMWH)	Maternal bleeding (major) Maternal bleeding (minor) Maternal HIT Maternal heparin-associated osteoporosis	RCT; observational study	None
5.1	Pregnant women undergoing Cesarean section	No prophylaxis	DVT Proximal DVT PE Fatal PE Symptomatic DVT/PE Major bleeding Minor bleeding	Control groups of RCTs; observational study	None
5.2	Pregnant women undergoing caesarean section	GCS IPC Aspirin UFH LMWH Danaparoid Pentasaccharide Coumarin derivatives Combined mechanical and pharmacologic prophylaxis	DVT Proximal DVT PE Fatal PE Symptomatic DVT/PE Major bleeding Minor bleeding	RCT; observational study	None
6.1	Pregnant women with acute VTE	UFH LMWH Thrombolysis	Recurrent DVT or PE during same pregnancy or in 6 wk postpartum	RCT; observational study	None
7.1	Pregnant women with history of DVT or PE (with or without thrombophilia†)	No antepartum or postpartum prophylaxis	Recurrent DVT or PE during pregnancy or in 6 wk postpartum	Control groups of RCTs; observational study	None
7.2	Pregnant women with history of DVT or PE (with or without thrombophilia†)	Antepartum UFH Antepartum LMWH Postpartum UFH Postpartum LMWH Postpartum coumarin derivatives Combined antepartum and postpartum prophylaxis	Recurrent DVT or PE during pregnancy or in 6 wk postpartum	RCT; observational study	None
8.1	Pregnant women with thrombophilia† and no prior history of DVT or PE	No antepartum or postpartum prophylaxis	DVT or PE during pregnancy or in 6 wk postpartum	Control groups of RCTs; observational study	None
8.2	Pregnant women with thrombophilia† and no prior history of DVT or PE	Antepartum UFH Antepartum LMWH Postpartum UFH Postpartum LMWH Postpartum coumarin derivatives Combined antepartum and postpartum prophylaxis	DVT or PE during pregnancy or in 6 wk postpartum	RCT; observational study	None

Table 1—*Continued*

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
9.1	Pregnant women with thrombophilia†	No prophylaxis	First trimester fetal loss Secone trimester fetal loss Third trimester fetal loss Intrauterine growth retardation Preeclampsia Placental abruption	Control groups of RCTs; observational study	Comorbid condition associated with pregnancy complications
9.2	Pregnant women with thrombophilia†	Antepartum UFH (with/without aspirin) Antepartum LMWH (with/without aspirin) Antepartum aspirin	First trimester fetal loss Third trimester fetal loss Second trimester fetal loss Intrauterine growth retardation Preeclampsia Placental abruption	RCT; observational study	Comorbid condition associated with pregnancy complications
10.1	Pregnant women without thrombophilia† with previous preeclampsia	Antepartum aspirin Antepartum UFH (with/without aspirin) Antepartum LMWH (with/without aspirin)	Recurrent preeclampsia	RCT; observational study	None
11.1	Pregnant women with mechanical heart valves	Coumarin derivatives throughout pregnancy UFH throughout pregnancy LMWH throughout pregnancy Coumarin derivatives substituted with UFH during first trimester (at or before 6 wk) Coumarin derivatives substituted with LMWH during first trimester (at or before 6 wk) Coumarin derivatives substituted with UFH during first trimester (after 6 wk) Coumarin derivatives substituted with LMWH during first trimester (after 6 wk) Aspirin throughout pregnancy	Maternal thromboembolism Maternal bleeding (minor) Maternal bleeding (major) Maternal death Congenital malformations Fetal loss	RCT; observational study	None

*PT = prothrombin time; GCS = graduated compression stockings; IPC = intermittent pneumatic compression stockings; RCT = randomized controlled trial.

†Thrombophilia is considered the presence of one or more of the following: antithrombin deficiency, protein C deficiency, protein S deficiency, activated protein C resistance, factor V Leiden, prothrombin G20210A mutation, hyperhomocysteinemia, homozygosity for the thermolabile variant of methylene tetrahydrofolate reductase (MTHFR), APLAs (nonspecific inhibitor/lupus anticoagulant or anticardiolipin antibody), elevated factor VIII levels, decreased protein Z level. Thrombophilias are to be considered on an individual basis for data search and extraction.

botic use during pregnancy, the risks of fetal teratogenicity and bleeding should be borne in mind.

2.1 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.[2–4] In a systematic review of the literature examining fetal and maternal outcomes of pregnant women with prosthetic valves,[4] Chan and colleagues provided pooled estimates of risks associated with the following commonly used 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. 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% confidence interval [CI], 4.6–8.9%) [Table 2].[4] The most common fetal anomaly seen was characteristic coumarin embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses. Limb hypoplasia has been reported in up to one third of cases of embryopathy.[5] Embryopathy

Table 2—*Frequency of Fetal Complications Reported With Various Anticoagulation Regimens Used in Pregnant Women With Prosthetic Valves (Section 2.1)

Anticoagulation Regimen	Spontaneous Abortions	Congenital Fetal Anomalies	Fetal Wastage
Vitamin K antagonists throughout with/without heparin at term	196/792 (24.8)	35/549 (6.4)	266/792 (33.6)
Heparin in first trimester, then vitamin K antagonists throughout with/without heparin near term			
Heparin use at/before 6 wk	19/129 (14.7)	0/108 (0.0)	21/129 (16.3)
Heparin use after 6 wk	9/56 (33.9)	4/36 (11.1)	20/56 (35.7)
Heparin use at unknown time in first trimester	19/45 (42.2)	2/30 (6.7)	20/45 (44.4)
Total	57/230 (24.8)	6/174 (3.5)	61/230 (26.5)
Heparin used throughout			
Adjusted-dose heparin	4/16 (25.0)	0/12 (0.0)	7/16 (43.8)
Low-dose heparin	1/5 (20.0)	0/5 (0.0)	2/5 (40.0)
Total	5/21 (23.8)	0/17 (0.0)	9/21 (42.9)
No anticoagulation			
Nothing	2/35 (5.7)	2/33 (6.1)	7/35 (20.0)
Antiplatelet agent	8/67 (11.9)	1/59 (1.7)	13/67 (19.4)
Total	10/102 (9.8)	3/92 (3.4)	20/102 (19.6)

*Data are presented as No./total (%). Data are from Chan et al.[4]

typically occurs after *in utero* exposure to vitamin K antagonists during the first trimester of pregnancy.[3] The magnitude of this risk varies widely among reports with estimates ranging from 0%[6–11] up to 29.6%.[12] Although the latter estimate is from a relatively large prospective study, it is likely to represent an overestimate because only two infants (5.7%) were described as having classic features of warfarin embryopathy, while the others had minor facial defects or facial bone features suggestive of embryopathy. The results of a recently published multicenter European study 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 up also suggests that the risk of coumarin embryopathy is not high.[13] Although the frequency of major birth defects after any first trimester exposure was increased compared to that seen in a control group of women counseled during pregnancy about exposures known to be nonteratogenic (4.8% vs 1.4%, respectively; odds ratio [OR], 3.86, 95% CI, 1.86–8.00), there were only two cases of embryopathy among 356 live births (0.6%). Both of these 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,[4] raising the possibility that vitamin K antagonists are safe with regard to embryopathy during the first 6 weeks of gestation, although there is a definite risk of embryopathy if coumarin derivatives are taken between 6 and 12 weeks of gestation.[3] Interestingly, in the European multicenter Teratology Information Services study, there were no cases of embryopathy in which vitamin K antagonists were discontinued before week 8 after the first day of the last menstrual period.[13]

Vitamin K antagonists have also been associated with CNS abnormalities after exposure during any trimester.[3] 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.[3] These complications are likely rare.[3,4] Although one cohort study reported that the use of coumarins during the second and third trimesters was not associated with major risks for abnormalities in growth and long-term development of offspring, the authors noted increased risk of minor neurodevelopmental problems (OR, 1.9; 95% CI, 1.1–3.4) in children exposed to coumarins in the second and third trimesters of pregnancy.[14] However, the clinical importance of these minor neurodevelopmental problems is uncertain because there were no differences in mean intelligence quotient or performance on tests for reading, spelling, and arithmetic between exposed and nonexposed children.[15]

In addition, vitamin K antagonists have been associated with fetal wastage[4,16] and can cause fetal hemorrhagic complications, likely because the fetal liver is immature and fetal levels of vitamin K dependent coagulation factors are normally 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[16] 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.[17] Although this strategy resulted in good neonatal and maternal outcomes, only thirty babies were delivered using this strategy. As well, it should be noted that cesarean section is not without risk and it not routinely recommended for other conditions associated with an increased risk of neonatal intracranial hemorrhage at the time of delivery (*eg*, immune thrombocytopenia purpura).

Given their potential for deleterious effects on the fetus, vitamin K antagonists should only be used during pregnancy when potential maternal benefits justify potential fetal risks. Although UFH and LMWH are as effective as vitamin K antagonists in the management of VTE (see section 6), vitamin K antagonists may be more effective than these agents in patients with mechanical prosthetic valves. Therefore, after discussing the risks and benefits with the patient, it would be reasonable to use vitamin K antagonists in pregnant women with high-risk valves (discussed in section 11).

Recommendations

2.1.1. For women receiving anticoagulation for the management of VTE who become pregnant, we recommend that vitamin K antagonists be substituted with UFH or LMWH (Grade 1A)**.**
2.1.2. For women with mechanical valves who become pregnant, we suggest either adjusted-dose bid LMWH or UFH throughout pregnancy or adjusted-dose bid LMWH or UFH until the thirteenth week with substitution by vitamin K antagonists until LMWH or UFH are resumed close to delivery (Grade 1C)**. In pregnant women with high-risk mechanical valves (*eg*, older-generation valve in the mitral position or history of thromboembolism), in whom concerns exist about the efficacy and safety of UFH or LMWH, we suggest the vitamin K antagonists over heparin with replacement by adjusted-dose bid UFH or LMWH close to delivery** (Grade 2C)**.**
Underlying values and preferences: The suggestion to utilize vitamin K antagonists during the first 12 weeks of pregnancy places similar value on avoiding maternal thromboembolic complications as on avoiding fetal risks.

2.2 Management of Women Receiving Long-term Vitamin K Antagonists Who Are Considering 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, two options can reduce the risk of warfarin embryopathy: (1) performance of frequent pregnancy tests and substitution of adjusted-dose UFH or LMWH for warfarin when pregnancy is achieved; or (2) replacement of vitamin K antagonists with UFH or LMWH 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. The second increases the duration of exposure to heparin and, therefore, is costly and exposes the patient to a higher risk of complications related to the use of UFH and LMWH. We suggest the first approach because it is convenient and appears to be safe.

Recommendation

2.2.1. For women requiring long-term vitamin K antagonists who are attempting pregnancy and are candidates for UFH or LMWH substitution, we suggest performing frequent pregnancy tests and substituting UFH or LMWH for vitamin K antagonists when pregnancy is achieved (Grade 2C)**.**
Underlying values and preferences: This recommendation places a higher value on avoiding the risks, inconvenience, and costs of UFH or LMWH therapy of uncertain duration while awaiting pregnancy, compared to minimizing the risks of early miscarriage associated with oral anticoagulant therapy.

2.3 UFH Exposure In Utero

UFH does not cross the placenta[18] and, therefore, does not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible. Several studies strongly suggest that UFH therapy is safe for the fetus[2,19] and should be used as necessary for maternal indications.

2.4 LMWH Exposure in Utero

As determined by measurement of anti-Xa activity in fetal blood, LMWH also does not cross the placenta.[20,21] There is no evidence of teratogenicity or risk of fetal bleeding.[22] Therefore, LMWH is safe anticoagulant choice for the fetus.

2.5 *Aspirin Exposure* in Utero

Although animal studies have shown that aspirin may increase the risk of congenital anomalies, data from human studies are conflicting. The most compelling data come from a metaanalysis of 14 randomized studies including a total of 12,416 women[23] that reported that low-dose (50 to 150 mg/d) aspirin therapy administered during the second and third trimesters of pregnancy to women at risk for preeclampsia was safe for the mother and fetus. The authors of this meta-analysis also reviewed observational studies including > 96,000 pregnancies and found no evidence of teratogenicity or long-term adverse effects of aspirin during pregnancy.[23]

The safety of aspirin ingestion during the first trimester remains uncertain. Another metaanalysis of eight studies (seven observational and one randomized) that evaluated the risk of congenital anomalies with aspirin exposure during the first trimester found no evidence of an increase in the overall risk of congenital malformations associated with aspirin use, suggesting that aspirin is safe even when used early in pregnancy.[24] In this study, however, aspirin use during the first trimester may have been associated with a two-fold increase in the risk for gastroschisis (OR, 2.37; 95% CI, 1.44–3.88), a rare anomaly that occurs in 3 to 6 of every 100,000 births in which the intestines herniate through a congenital defect in the abdominal wall on one side of the umbilical cord.[24] However, the reliability of this risk estimate is questionable as the use of other drugs, the type of control subjects selected, and failure to definitively confirm the diagnosis in all patients could have biased these results.

Available evidence suggests that low-dose aspirin during the second and third trimester is safe for the fetus and clinicians should use this agent as necessary for maternal indications. Although the safety of aspirin ingestion during the first trimester remains uncertain, there is no clear evidence of harm to the fetus and, if fetal anomalies are caused by early aspirin exposure, they are very rare. If the indication for aspirin is clear and there is no satisfactory alternative agent, clinicians should offer first-trimester patients aspirin.

2.6 *Danaparoid Exposure* in Utero

Consistent with investigations of danaparoid placental transfer in pregnant guinea pigs that indicated negligible movement across the placenta,[25] two case reports in which clinicians used danaparoid to treat heparin-induced thrombocytopenia (HIT) in pregnancy reported no detectable anti-Xa activity in fetal cord plasma.[26,27] A review of 51 pregnancies in 49 danaparoid-treated patients reported three fetal deaths, but all were associated with maternal complications antedating danaparoid use.[28] Thus, the available literature suggests that there is no demonstrable fetal toxicity with maternal danaparoid use. However, the quality of evidence available to support that claim is low.

2.7 *Direct Thrombin Inhibitor Exposure* in Utero

Investigations have documented placental transfer of r-hirudin in rabbits and rats.[29,30] Although small numbers of case reports of successful outcomes with r-hirudin use in pregnancy have been published,[29,31,32] there are insufficient data to evaluate its safety in this setting. The use of direct thrombin inhibitors in pregnant women should be limited to those with severe allergic reactions (including HIT) to heparin who cannot receive danaparoid.

2.8 *Pentasaccharide Exposure* in Utero

Although no placental passage of fondaparinux was demonstrated in an *in vitro* human cotyledon model,[33] anti-factor Xa activity (at approximately one tenth the concentration of maternal plasma) was found in the umbilical cord plasma in newborns of five mothers treated with fondaparinux.[34] Although there have been reports of the successful use of this agent in pregnant woman,[35,36] the quality of evidence supporting or recommending against the use of fondaparinux during pregnancy is weak and potential deleterious effects of fondaparinux on the fetus cannot be excluded. Thus, clinicians should avoid the use of fondaparinux during pregnancy whenever possible and reserve its use for those pregnant women with HIT or a history of HIT who cannot receive danaparoid.

2.9 *Thrombolysis During Pregnancy*

Investigations with 131 I-labeled streptokinase showed minimal transplacental passage[37] and placental transfer of tissue plasminogen activator, a finding consistent with their large molecular size. Concerns about the use of thrombolytic therapy during pregnancy center on its effect on the placenta (*ie*, premature labor, placental abruption, fetal demise). Although there have been several reports of successful thrombolysis in pregnancy with no harm to the fetus,[38,39] its safety in this setting is unclear and the use of thrombolytic therapy in pregnancy is best reserved for life-threatening maternal thromboembolism.

3.0 Use of Anticoagulants in Nursing Women

Clinicians considering antithrombotic therapy in breast-feeding women must consider risks to the

neonate. For most agents, research data are limited. 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, it must also be absorbed from the infant's gut. Drugs that are poorly absorbed orally 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.[40]

Despite a lack of data suggesting any harmful effect to breast-feeding infants, many obstetricians remain reluctant to prescribe warfarin to lactating women. These concerns might represent extrapolations from warfarin's fetopathic effects and theoretical concerns that less polar, more lipophilic oral anticoagulants rarely utilized in North America (eg, phenindione and anisindione) might be excreted into breast milk.[41] 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 (Table 3).[42,43] Therefore, the use of warfarin in women who require postpartum anticoagulant therapy is safe.

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.[44] In a case series of 15 women receiving 2,500 IU of LMWH after cesarean section, there was evidence of excretion of small amounts of LMWH into the breast milk in 11 patients (Table 3).[45] However, given the very low bioavailability of heparin ingested orally, there is unlikely to be any clinically relevant effect on the nursing infant.

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.[29] As danaparoid is not absorbed after oral intake, it is unlikely that any anticoagulanteffect would appear in breastfed infants.

In a single case report, no hirudin was detected in the breast milk of a nursing mother with a therapeutic plasma hirudin level.[46] Enteral absorption of r-hirudin appears to be low.[30] Therefore, it is unlikely that exposed infants would experience a significant anticoagulant effect, even if small amounts of hirudin appear in breast milk. It is not known whether or to what extent fondaparinux is excreted in breast milk.

Recommendations

3.0.1. For lactating women using warfarin or UFH who wish to breastfeed, we recommend continuing these medications (Grade 1A)**.**

3.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, we suggest continuing these medications (Grade 2C)**.**

3.0.3. For breastfeeding women, we suggest alternative anticoagulants rather than pentasaccharides (Grade 2C)**.**

Table 3—*Prospective Studies of the Effect of Maternal Anticoagulant Therapy on Breastfed Infants: Clinical Description and Results (Sections 3.1, 3.3)**

Study/Yr	Interventions	Patients Analyzed, No./Total	Length of Follow-up After Delivery	Infant Hemorrhage, No./Total	Presence in Breast Milk, No./Total	Effect in Infant Blood, No./Total	Comments
Orme et al[42]/1977	Warfarin exposure during breastfeeding	Breast-fed infants: 7/7	Up to 10 d	0/7	Warfarin: 0/7	Warfarin: 0/7	Warfarin levels measured by chromatography (lower limit of detection: 0.08 μmol/L)
McKenna et al[43]/1977	Warfarin exposure during breastfeeding	Breast-fed infants: 2/2	#1: 56 d #2: 130 d	0/2	Warfarin: 0/2	Elevated PT: 0/2	Presence of warfarin in breast milk detected by spectrophotometry
Richter et al[45]/2001	LMWH exposure during breastfeeding (maternal dose dalteparin 2,500 IU SC)	Breast-fed infants: 15/15	Up to 8 d	NR	Anti-Xa LMWH level: 11/15 (range 0.007–0.028 IU/mL)	NR	Therapeutic anti-Xa LMWH level: 0.5–1.5 IU/mL, 4–6 h after injection

*NR = not recorded. See Table 1 for expansion of abbreviations. The methodological quality description portion of the table can be found in the online version of this article as a data supplement.

Table 4—*Randomized Trials and Prospective Cohort Studies of UFH and LMWH in the Prevention of VTE in Pregnant Women Undergoing Cesarean Section: Clinical Description and Results (Section 5.2)***

Study/Yr	Interventions	Patients Analyzed, No./Total	Length of Follow-up After Cesarean Section	DVT, No./Total	PE, No./Total	Bleeding, No./Total	Comments
Hirota et al[83]/ 2005	Dalteparin 60 IU/kg SC/d	Control: 16/16 Low risk: 13/13 High risk: 24/24	24 to 72 h	Control: 0/16 Low risk: 0/13 High risk: 0/24	Control: 0/16 Low risk: 0/13 High risk: 0/24	Control: 0/16 Low risk: 0/13 High risk: 0/24	Primary outcome: laboratory markers of plasma coagulation
Ellison et al[84]/ 2001	Dalteparin 5,000 IU SC/d; enoxaparin 4,000 IU SC/d; tinzaparin 50 IU/ kg SC/d	Dalteparin: 10/10 Enoxaparin: 10/10 Tinzaparin: 10/10	5 d	Dalteparin: 0/10 Enoxaparin: 0/10 Tinzaparin: 0/10	Dalteparin: 0/10 Enoxaparin: 0/10 Tinzaparin: 0/10	Dalteparin: 0/10 Enoxaparin: 0/10 Tinzaparin: 0/10	Primary outcome: laboratory markers of LMWH activity
Burrows et al[85]/ 2001	Dalteparin 2,500 IU SC/d; placebo: saline solution SC	Dalteparin: 39/39 Placebo: 37/37	6 wk	Dalteparin: 1/39 (2.7%) Placebo: 0/37 RR: 2.85 95% CI: 0.12–67.83	Dalteparin: 0/39 Placebo: 0/37	Dalteparin: 0/37 Placebo: 0/39	
Gates et al[86]/ 2004	Enoxaparin: 40 mg SC/d; placebo: saline solution SC	Enoxaparin 66/70 Placebo: 68/70	6 mo	Enoxaparin: 0/66 Placebo: 0/68	Enoxaparin: 1/66 (1.5%) Placebo: 0/68 RR: 3.09; 95% CI: 0.13–74.51	Enoxaparin: 0/66 Placebo: 0/68 (major bleeding)	
Hill et al[87]/ 1988	UFH 5,000 U SC q 12 h starting 1 h before surgery placebo: saline solution SC	UFH: 25/25 Placebo: 25/25	6 d	UFH: 0/25 Placebo: 0/25	UFH: 0/25 Placebo: 0/25	UFH: 3/25 (12.0%) Placebo: 3/25 (12.0%) [≥ 1,000 mL) RR: 1.0; 95% CI: 0.22–4.49	
Gibson et al[88]/ 1998	UFH 7,500 U SC q 12 h enoxaparin 20 mg SC/d; enoxaparin 40 mg SC/d	UFH: 6/6 Enoxaparin 20 mg: 6 Enoxaparin 40 mg: 5	24 h	UFH: 0/6 Enoxaparin: 0/11	UFH: 0/6 Enoxaparin: 0/11	UFH: 0/6 Enoxaparin: 0/11	

*SC = subcutaneous. The methodologic quality description portion of the table can be found in the online version of this article as a data supplement.

4.0 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 HIT, heparin-associated osteoporosis, and pain at injection sites for heparin-related compounds.

4.1 UFH Therapy

During pregnancy, UFH is 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 IV by continuous infusion with dosage adjustment to achieve a target therapeutic activated partial thromboplastin time (aPTT) or by twice-daily subcutaneous injection in doses sufficient to achieve a therapeutic aPTT 6 h after injection. During pregnancy, the aPTT response to UFH is often attenuated, likely because of increased levels of heparin-binding proteins, factor VIII, and fibrinogen.[47] This causes a "blunting" of the aPTT response relative to the heparin level and a resultant increased requirement for UFH. 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 cohort study,[19] the rate of major bleeding in pregnant women treated with UFH was 2%, which is consistent with reported rates of bleeding associated with heparin therapy in nonpregnant patients[48] and with warfarin therapy[49] when used for the treatment of deep vein thrombosis (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.[50] The mechanism for this prolonged effect is unclear. A prolonged anticoagulant effect with IV-administered UFH has not been noted in pregnant women; however, data with this method of administration in pregnancy are scarce.

Approximately 3% of nonpregnant patients receiving UFH have immune IgG-mediated thrombocytopenia (HIT), which may lead to extension of preexisting thrombosis or new onset of venous or arterial thrombosis.[51] Although it is reasonable to expect that the frequency of HIT in pregnant and postpartum women exposed to UFH would be similar, insufficient data exist to confirm or refute this observation. HIT should be differentiated from an early, benign, transient thrombocytopenia that can occur with initiation of UFH and from pregnancy-specific disorders including incidental thrombocytopenia of pregnancy[52] and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Diagnosing HIT is often difficult because immune assays are nonspecific and the more specific platelet-activation assays are not widely available and turnaround times are slow. HIT should be suspected when the platelet count falls to $< 100 \times 10^9$/L or $< 50\%$ of the baseline value 5 to 15 days after commencing heparin or sooner with recent heparin exposure.[51] The diagnosis, prevention, and treatment of HIT are described in the chapter "Treatment and Prevention of Heparin-Induced Thrombocytopenia." 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[53] that does not cross the placenta[25–27] and has low cross-reactivity with UFH[54] and, therefore, rarely produces HIT.

Long-term treatment with UFH has been reported to cause osteoporosis in both laboratory animals and humans.[55–63] In animal studies, UFH causes a dose-dependent loss of cancellous bone through decreasing rates of bone formation and increased bone resorption.[61] Animal models demonstrating that heparin is sequestered in the bone for extended periods also suggest that heparin-induced osteoporosis may not be rapidly reversible.[63] 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 approximately 2 to 3% of the patient population and significant reductions of bone density have been reported in up to 30%.[55,56] A small study (n = 40) reported an even higher percentage of fractures (15%) when older nonpregnant patients were treated with twice-daily subcutaneous injections of 10,000 U UFH for a period of 3 to 6 months.[59]

4.2 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[64,65] and acute coronary syndromes,[66,67] as well as for prophylaxis in high-risk patients.[68] Retrospective analyses and systematic reviews suggest that the incidence of bleeding in pregnant women receiving LMWH is low.[22,69,70] A review of LMWH use in 486 pregnancies identified a frequency of minor bleeding of 2.7% and no major hemorrhagic events.[69] In a more recent systematic review of 64 studies reporting 2,777 pregnancies, 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%).[70] Although HIT can occur with LMWH therapy, the risk appears lower with LMWH than with UFH[51] and no confirmed cases were identified in these two large reviews.[69,70]

Several lines of evidence suggest that LMWHs have a lower risk of osteoporosis than UFH. When rats were treated with UFH or LMWH (tinzaparin), both treatments were associated with a dose-dependent decrease in cancellous bone volume but LMWH caused significantly less bone loss than UHF.[62] In a study by Monreal and colleagues[59] in which 80 patients (men and women with a mean age of 68 years) with DVT were treated with either 5,000 U subcutaneously bid of dalteparin or 10,000 U subcutaneously bid of UFH for a period of 3 to 6 months, the risk of vertebral fractures was higher in those receiving UFH (6 of 40 patients [15%]; 95% CI, 6–30%) than in those receiving dalteparin (1 of 40 patients [3%]; 95% CI, 0–11%). In another randomized trial, 44 pregnant women were allocated to prophylactic doses of dalteparin (n = 21) or UFH

(n = 23)[60] and bone density in the lumbar spine was measured for up to 3 years after delivery. Bone density did not differ between women receiving dalteparin and untreated patients but was significantly lower in those receiving UFH compared to both those who were not treated and those who received dalteparin. On multiple logistic regression analysis, the type of heparin used was the only independent factor associated with reduced bone mass. Similar results were reported in a prospective observational study in which 55 pregnant women treated with prophylactic LMWH and aspirin and 20 pregnant untreated volunteers had dual energy radiograph absorptiometry scans of the lumbar spine performed within 6 months prior to conception and within 6 weeks of delivery.[71] Both groups showed a loss in lumbar spine bone mineral density by the end of pregnancy, but there was no statistically significant difference in bone loss between the two patient populations, suggesting that bone loss associated with prophylactic LMWH therapy is not different from normal physiologic losses during pregnancy.

Recommendation

4.2.1. For pregnant patients, we suggest LMWH over UFH for the prevention and treatment of VTE (Grade 2C)**.**

5.0 VTE Following Cesarean Section

The frequency of cesarean delivery is increasing in developed countries and rates in excess of 30% are now commonplace. Available data suggest that this mode of delivery is associated with an increased relative risk of fatal and nonfatal VTE, with the risk being highest following emergency procedures.[72–74]

5.1 Risk of VTE Following Cesarean Section

In a population-based study conducted before the implementation of guidelines for postpartum thromboprophylaxis in which outcome frequencies were based on routinely collected hospital record data, the incidence of DVT after cesarean section was reported to be 0.424/1,000 vs 0.173/1,000 following vaginal delivery.[72] In the same study, the risk of pulmonary embolism (PE) was also higher after cesarean delivery, complicating almost 0.4/1,000 such deliveries.[72] In a Swedish study that also utilized health record information, the adjusted relative risk (RR) of PE associated with cesarean section compared to that with vaginal delivery was 6.7 (95% CI, 4.5–10.0).[75] These data are consistent with those from a retrospective review of objectively confirmed events in a hospital population in the United States in which the frequency of VTE was reported as 0.521/1,000 cesarean sections.[74]

When cesarean section is performed emergently, the risk of VTE is approximately double that of an elective procedure.[72] Further, interaction between risk factors has been noted, with the combination of age > 35 years and emergency cesarean delivery being associated with an incidence of DVT of approximately 1.2/1,000 deliveries and that for PE of 1/1,000 deliveries.[72] In a single-center Norwegian cohort study in which 5 of 1,067 women undergoing cesarean section had symptomatic, objectively confirmed VTE (0.47%), all the affected women had additional risk factors including twin pregnancy, obesity, severe preeclampsia, re-operation, immobilization, and placenta previa.[76]

Studies based on hospital records and disease coding have significant limitations[77] that may result in an underestimation of the true incidence of VTE. Few studies have screened consecutive patients objectively for VTE postpartum. In the Norwegian study described above, 59 low-risk women undergoing elective cesarean section underwent screening for DVT using triplex ultrasonography (compression, color Doppler and spectral Doppler) 2 to 5 days after delivery and followed up for 6 weeks; none had symptomatic or asymptomatic VTE (95% CI, 0–6.1%).[76]

Others have suggested that pelvic MRI venography (MRV) is a better surrogate measure for DVT. A recent clinical trial of 15 women considered to be at moderate or high risk of DVT after cesarean section in which screening for DVT was performed using compression ultrasonography of the proximal veins and pelvic MRV reported that 46% (95% CI, 21–73%) had evidence of pelvic vein thrombosis, while none had a positive ultrasound assessment of the legs.[78] None of the affected women were symptomatic. Although these data suggest that asymptomatic pelvic thrombosis may be common after cesarean section in women with additional risk factors, the clinical significance of these radiologic findings is not clear.

Although cesarean section is likely to be a risk factor for VTE, the level of risk for symptomatic events attributable to cesarean section itself appears very modest and similar to that seen in low-risk surgical patients for whom no routine thromboprophylaxis other than mobilization is recommended (*ie*, frequency of proximal DVT: 0.4%; frequency of symptomatic PE: 0.2%).[79] Although data from MRV-based screening studies suggests a substantial risk of asymptomatic pelvic vein thrombosis, the data are limited to one study and the natural history of these types of thrombi is unknown. Based on the small

number of associated clinically evident events, routine thromboprophylaxis is not justified and cannot be recommended on the basis of cesarean section alone.

Limited data do suggest that the presence of additional risk factors may increase the risk of VTE associated with cesarean section. The quantification of risk when multiple factors are combined is not clearly established. However, the addition of multiple other risk factors (*ie*, increased age, prior VTE, obesity, thrombophilia, lower limb paralysis, immobilization, extended surgery such as hysterectomy, preeclampsia, and comorbid medical conditions such as heart failure) is likely to place the patient at moderate to high risk of VTE.

Recommendations

5.1.1. We suggest that a thrombosis risk assessment be performed in all women undergoing cesarean section to determine the need for thromboprophylaxis (Grade 2C)**.**

5.1.2. In patients without additional thrombosis risk factors undergoing cesarean section, we recommend against the use of specific thromboprophylaxis other than early mobilization (Grade 1B)**.**

5.2. Thromboprophylaxis Following Cesarean Section

For many years, guidelines in the United Kingdom have advocated the use of prophylaxis following cesarean section in women with additional risk factors,[80,81] and the use of thromboprophylaxis with LMWH following cesarean section is now widespread in Europe. These recommendations however, are based on expert opinion and consensus rather than good quality clinical trials. To date, no adequately powered clinical trials of thromboprophylaxis following cesarean section have been conducted.[82] One prospective cohort[83] and six randomized studies[84–89] have been published (Tables 4, 5). Of the randomized trials, the primary outcome was VTE in four[85,86,88,89]: two compared LMWH with placebo,[85,86] one evaluated UFH vs placebo,[87] one randomized patients to either LMWH or UFH,[88] and one compared hydroxyethyl starch (an intervention that is no longer utilized) with placebo.[89] The sample sizes of all these trials were small. The trial evaluating UFH against placebo enrolled 50 patients,[87] while that comparing UFH and LMWH recruited < 20.[88] One pilot study of 76 patients comparing LWMH vs placebo after cesarean section, reported a 26% recruitment rate and a DVT frequency of 1.3% (95% CI, 0.03–7.1%).[85] Although the

Table 5—*Randomized Trials and Prospective Cohort Studies of UFH and LMWH in the Prevention of VTE in Pregnant Women Undergoing Cesarean Section: Summary Evidence Profile (Section 5.2)*

	Quality Assessment							Summary of Findings				
								Patients, No./Total		Effect		
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	LMWH	Placebo	RR (95% CI)	Events Prevented per 1,000 Treated	Quality
DVT												
2*	Randomized controlled trial	No serious limitations	No important inconsistency	No problem	Large imprecision (−2)†	None	No strong association	1/105 (1.0%)	0/105	2.85 (0.12–67.83)‡	Not significant§	Low
Maternal bleeding												
2*	Randomized controlled trial	No serious limitations	No important inconsistency	No problem	Large imprecision (−2)†	None	No strong association	0/105	0/105	Not calculated	Not significant§	Low

*Includes Burrows et al[85]/2001 and Gates et al[86]/2004.
†95% CI includes no effect and < 10 events.
‡Based on one study only: Burrows et al[85]/2001.
§95% CI includes no effect. Events per 1,000 treated not calculated.

authors of this pilot study concluded that a full study was feasible, the difficulties of conducting such a trial were highlighted in another pilot study of LMWH vs placebo in which recruitment was slow (141 women at eight hospitals over the course of two years) and the overall event rate was low (0.7%).[86] Based on their pilot data, the authors of this second study calculated that approximately 8,000 hospital-months of recruitment would be required to demonstrate the effectiveness of LMWH prophylaxis after cesarean section.

In the absence of high-quality trial data evaluating optimal thromboprophylaxis after cesarean section, others have utilized decision analyses to determine optimal prophylactic strategies. Quiñones and colleagues modeled and compared four approaches: universal subcutaneous UFH prophylaxis, UFH prophylaxis for patients with genetic thrombophilia, pneumatic compression stockings, and no prophylaxis.[90] Outcomes included VTE, HIT, HIT-related thrombosis, and major maternal bleeding. The use of pneumatic compression stockings was the strategy with the lowest number of adverse events, while universal prophylaxis with subcutaneous UFH was associated 13 cases of HIT-induced thrombosis and bleeding per VTE prevented. This model has substantial limitations. Data used to derive risk probability estimates were largely derived from studies that included nonpregnant patients, and a cost-analysis component was not included. A strategy utilizing LMWH prophylaxis was not evaluated, and the negligible risk of HIT associated with LMWH use in this population would be expected to impact on this model.[70,91] Given the absence of data from controlled trials in this population, recommendations regarding thromboprophylaxis are by necessity based on extrapolation from other patient populations.

Recommendations

5.2.1. For women considered at increased risk of VTE after cesarean section because of the presence at least one risk factor in addition to pregnancy and cesarean section, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH or UFH) or mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression) while in hospital following delivery (Grade 2C)**.**

5.2.2. For women with multiple additional risk factors for thromboembolism who are undergoing cesarean section and are considered to be at very high risk of VTE, we suggest that pharmacologic prophylaxis be combined with the use of graduated compression stockings and/or intermittent pneumatic compression (Grade 2C)**.**

5.2.3. For selected high-risk patients in whom important risk factors persist following delivery, we suggest extended prophylaxis (up to 4 to 6 weeks after delivery) following discharge from hospital (Grade 2C)**.**

6.0 VTE During Pregnancy

PE remains the major cause of maternal mortality in the Western world[73,92] and VTE in pregnancy is an important cause of maternal morbidity.[93] 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 1.3 episodes per 1,000 deliveries.[72,74,93–96] Although these rates are low, they represent a fivefold to tenfold increase in risk compared to those reported for nonpregnant women of comparable age. A meta-analysis showed that two-thirds of DVT occur antepartum, with these events distributed relatively equally throughout all three trimesters.[97] In contrast, 43 to 60% of pregnancy-related episodes of PE appear to occur in the 4 to 6 weeks after delivery.[74,96] Since 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.

6.1 Treatment of VTE During Pregnancy

Based on the safety data for both mother and fetus, LMWH is the preferred drug for the treatment of VTE during pregnancy. Metaanalyses of well-designed randomized trials comparing IV UFH and subcutaneous LMWH for the acute treatment of DVT[64] and PE[65] in the nonpregnant population show that LMWH is at least as safe and effective as UFH. Additional studies in the nonpregnant population demonstrate that long-term LMWH (and UFH) are as effective and safe as vitamin K antagonists for the prevention of recurrent VTE.[98–100]

Clinicians selecting UFH can use one of two alternatives: (1) initial IV therapy followed by adjusted-dose subcutaneous UFH given q12h or (2) twice-daily adjusted-dose subcutaneous UFH can be used for initial and long-term treatment. With subcutaneous therapy, UFH doses should be adjusted to prolong a mid-interval (6 h after injection) aPTT into therapeutic range. LMWH is the preferred option for most patients because of its better bioavailability, longer plasma-half-life, more predictable dose response, and improved safety profile with respect to osteoporosis and thrombocytopenia compared to UFH.[68,70] Further, LMWH is a more convenient

Table 6—*Risk of Early Loss in Women With Thrombophilia (Section 9.1)

Type of Thrombophilia	Thrombophilia	No Thrombophilia	OR (95% CI)
Factor V Leiden (homozygous)	37/76	484/1,010	2.71 (1.32–5.58)
Factor V Leiden (heterozygous)	172/243	1,632/2,689	1.68 (1.09–2.58)
Prothrombin gene mutation (heterozygous)	53/75	657/1,356	2.49 (1.24–5.00)
MTHFR C677T (homozygous)	53/75	534/907	1.40 (0.77–2.55)
Antithrombin deficiency	2/8	54/196	0.88 (0.17–4.48)
Protein C deficiency	2/3	34/73	2.29 (0.20–26.43)
Protein S deficiency	3/4	33/72	3.55 (0.35–35.72)
Anticardiolipin antibodies	127/149	869/1,956	3.40 (1.33–8.68)
Lupus anticoagulantsb (nonspecific inhibitor)	59/107	581/1,728	2.97 (1.03–9.76)
Hyperhomocysteinemia	33/37	128/235	6.25 (1.37–28.42)

*Data are presented as No./total. Data derived from Robertson et al.[128]

option because, unlike UFH, LMWH does not require frequent aPTT monitoring. If LMWH is used, a weight-adjusted dose 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 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.[101] On the basis of small studies showing the need for dose-escalation to maintain "therapeutic" anti-Xa LMWH levels,[102,103] some advocate the performance of perform periodic (*eg*, every 1 to 3 months) anti-factor Xa LMWH levels 4 to 6 h after injection with dose-adjustment to maintain a therapeutic anti-Xa level (0.6 to 1.0 U/mL if a twice-daily regimen is used; slightly higher 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.[104] In the absence of large studies using clinical endpoints demonstrating that there is an optimal "therapeutic anti-Xa LMWH range" or that dose-adjustments increase the safety or efficacy of therapy; any of these approaches is reasonable and definitive advice cannot be provided. Data regarding platelet count monitoring for detection of HIT and the role of compression stockings in the acute management of DVT are contained in the chapters "Treatment and Prevention of Heparin-Induced Thrombocytopenia" and "Antithrombotic Therapy for Venous Thromboembolic Disease," respectively.

It remains unclear whether the dose of UFH or LMWH can be reduced after an initial phase of therapeutic anticoagulation. It has been suggested that full-dose anticoagulation should be maintained throughout pregnancy and the puerperium because of the ongoing risk of recurrent VTE during this time period. However, regimens in which the intensity of LMWH is reduced later during the course of therapy to an intermediate-dose regimen[59] or 75% of a full treatment dose[100] have been used successfully in the nonpregnant population. A similar approach when using LMWH in pregnancy may reduce the 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.

In order to avoid an unwanted anticoagulant effect during delivery (especially with neuroaxial anesthesia) in women receiving adjusted dose subcutaneous UFH[50] or LMWH, UFH or LMWH can be discontinued 24 to 36 h before elective induction of labor or cesarean section. If spontaneous labor occurs in fully anticoagulated women, neuroaxial anesthesia should not be employed. In women receiving subcutaneous UFH, careful monitoring of the aPTT is required and, if it is markedly prolonged, protamine sulfate may be required to reduce the risk of bleeding. If available, anti-Xa LMWH levels should be checked in women treated with LMWH. If bleeding occurs, protamine sulfate may provide partial neutralization.[105]

Women with a very high risk for recurrent VTE (*eg*, proximal DVT or PE within 4 weeks of delivery) can be switched to therapeutic IV UFH, which is then discontinued 4 to 6 h prior to the expected time of delivery. With this approach, the duration of time without therapeutic anticoagulation can be shortened considerably. Alternatively, a temporary inferior vena caval filter can be inserted and removed postpartum.

There are no appropriately designed trials to guide the duration of postpartum anticoagulation for women diagnosed with VTE during pregnancy. In general, at least 6 months of anticoagulant therapy

with treatment continued until at least 6 weeks postpartum is a reasonable duration.

Recommendations (see "Summary of Recommendations" for definitions of dosing regimens)

6.1.1. For pregnant women with acute VTE, we recommend initial therapy with either adjusted-dose subcutaneous LMWH or adjusted-dose UFH (IV bolus, followed by a continuous infusion to maintain the aPTT within the therapeutic range or subcutaneous therapy adjusted to maintain the aPTT 6 h after injection into the therapeutic aPTT range) for at least 5 days (Grade 1A).
6.1.2. For pregnant women with acute VTE, after initial therapy, we recommend that subcutaneous LMWH or UFH should be continued throughout pregnancy (Grade 1B).
6.1.3. 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 6 months) [Grade 2C].
6.1.4. For pregnant women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuation of the heparin at least 24 h prior to elective induction of labor (Grade 1C).

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

Compared to individuals without a history of VTE, patients with previous VTE are at increased risk of further episodes of DVT and PE.[106] Women with a history of VTE are also believed to have a higher risk of VTE in subsequent pregnancies.[107] Thromboprophylaxis during pregnancy is problematic because it involves long-term parenteral UFH or LMWH. Both are expensive, inconvenient and painful to administer and are associated with risks for bleeding, osteoporosis, and HIT; although these complications, particularly HIT, are very uncommon with LMWH.[70,91] Therefore, rational administration of prophylaxis depends on identifying those women who have an increased risk of thrombosis and accurately quantifying this risk. The threshold for recommending postpartum prophylaxis is lower than for antepartum prophylaxis due to the shorter length of required treatment (*ie*, 6 weeks), the higher average daily risk of VTE in the postpartum period,[97] and the safety of warfarin during this time period, even if the mother is breastfeeding.[42,43] The relatively equal distribution of DVT throughout all three trimesters[97] suggests that when antepartum prophylaxis is utilized, it should be instituted early in the first trimester.

7.1 Prior VTE and Pregnancy

The extent to which pregnancy influences the risk of recurrent VTE remains somewhat uncertain. In a retrospective study of 109 women who had at least one pregnancy without receiving thrombosis prophylaxis after an episode of VTE, recurrence rates per 100 patient-years were 10.9% during and 3.7% outside of pregnancy (RR during pregnancy, 3.5; 95% CI, 1.6–7.8).[107] Previous estimates of the rate of recurrent venous thrombosis during pregnancy in women with a history of VTE varied between zero and 13%.[108–111] The higher risk estimates come from retrospective studies of nonconsecutive patients in which objective testing was not used routinely to confirm the diagnosis of recurrent VTE, thereby resulting in a substantial overdiagnosis of recurrence.[110,111] In contrast, the lower estimates come from prospective, albeit small (n = 20, n = 59), studies.[108,109]

In order to obtain a reliable estimate of the true incidence of recurrence in women with prior VTE, Brill-Edwards and colleagues performed a prospective study of 125 pregnant women with a single previous episode of objectively diagnosed VTE.[112] Antepartum heparin was withheld and anticoagulants (usually warfarin with a target INR of 2.0 to 3.0 with an initial short course of UFH or LMWH) were given in the postpartum period for 4 to 6 weeks. Three women had antepartum recurrences (2.4%; 95% CI, 0.2–6.9%), and three women had recurrent VTE postpartum. *Post hoc* subgroup analysis identified women without thrombophilia who had a temporary risk factor 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%). Antepartum recurrences occurred in 3 of 51 women with abnormal thrombophilia testing and/or a previous episode of thrombosis that was unprovoked (5.9%; 95% CI, 1.2–16.0%).

Some have suggested that the advanced median gestational age at enrollment (approximately 15 weeks) and the exclusion of women with known thrombophilia in the Brill-Edwards study might result in an underestimate of the true risk of pregnancy-related recurrent VTE. In a subsequently published retrospective cohort study of 159 women with at least one pregnancy after VTE, the probability of antepartum VTE in those not given antepartum prophylaxis was 6.2% (95% CI, 1.6–10.9%), while that for postpartum VTE was 6.5% (95% CI, 3.5–11.9%).[113] In this study, the presence or absence of temporary risk factors or of a definable thrombophilia did not appear to influence the risk of recurrent VTE associated with pregnancy. The retrospec-

tive nature of this study, differences in study population (including the inclusion of women with more than one prior episode of VTE) and failure to independently adjudicate recurrent events might account for the higher risk of recurrence in this study. However, in both studies, the overall risk of antepartum recurrent VTE was < 10% and CI's around the risk estimates are overlapping.

7.2 Prevention of Recurrent VTE in Pregnant Women

Although available data suggests that women with prior VTE have an increased risk of recurrence during pregnancy, the absolute recurrence rates both overall and in certain patient subgroups are unknown. There have been no large clinical trials assessing the role of prophylaxis in pregnant women with previous VTE. To date, only two randomized trials evaluating the safety and efficacy of prophylaxis (compared to placebo or no treatment) in pregnant women with prior VTE have been published.[86,109] Both have major methodologic weaknesses, including sample sizes (n = 40 and n = 16) too small to detect significant differences in the incidence of VTE.

As a result, recommendations are primarily based on the risk estimates reported by Brill-Edwards and colleagues,[112] and antepartum prophylaxis appears unwarranted in women without thrombophilia whose previous episode of thrombosis was associated with a temporary risk factor. However, this decision should be considered on an individual basis, taking all the woman's risk factors for VTE and patient preference into account. There is a great need for further studies are to confirm the estimates reported by Brill-Edwards and colleagues and to determine whether prophylaxis is warranted in patients with laboratory thrombophilia and/or a previous episode of idiopathic thrombosis.

Given its benefits compared with UFH, LMWH is generally the preferred agent for prophylaxis. A small pilot study in which pregnant patients with prior VTE were randomized to antenatal LMWH or placebo,[86] a small randomized trial in which LMWH prophylaxis was compared with UFH in pregnant women with prior or acute VTE,[114] as well as in several recent cohort studies all reported low VTE rates with the use of prophylactic once-daily LMWH.[60,115–122] For prophylaxis of VTE during pregnancy, several dose regimens of LMWHs have been used, including subcutaneous enoxaparin 40 mg q24h,[60,86] dalteparin 5,000 U q24h,[114] and dose-adjusted LMWH to achieve a peak anti-Xa level of 0.2 to 0.6 U/mL.[120–122] Although all of the studies reported low recurrence rates, most were nonrandomized studies and, therefore, the recurrence rates might have been low without prophylaxis. Further, it is difficult to draw reliable conclusions from the placebo-controlled trial, given its small sample size (n = 16).[86]

The need to adjust LMWH dosing according to anti-Xa levels remains controversial. The increased renal clearance of LMWH during pregnancy has led some to suggest that clinicians undertake periodic monitoring of the anticoagulant effect because anticoagulant activity may decrease as pregnancy progresses. On the other hand, the appropriate "therapeutic range" for prophylaxis is uncertain, and it has not been shown that dose adjustment to attain a specific anti-Xa level increases safety or efficacy of prophylaxis. Moreover, routine monitoring of anti-Xa levels is expensive and inconvenient and its reliability is compromised by interassay and instrument variability of anti-Xa results.[123,124]

Subcutaneous UFH, 5,000 U q12h, is effective and safe for the prevention of VTE in high-risk nonpregnant patients,[125] and some recommend its use in pregnant patients. However, there is concern that this low dose may be insufficient in high-risk situations because it does not reliably produce detectable heparin levels. There are also published data that intermediate intensity heparin therapy, in doses that produce plasma heparin levels (measured as anti-factor Xa activity) of 0.1 to 0.2 U/mL, is associated with low recurrence rates in pregnant women with previous VTE.[56] Thus, where UFH is employed for prophylaxis in pregnancy, higher doses are often used, such as 10,000 U bid. Until comparative studies are performed, it is not possible to make definitive recommendations about which prophylactic regimen of UFH should be used (if active prophylaxis is chosen).

Repeated screening during the antepartum period with noninvasive tests for DVT, such as compression ultrasonography, is not justified for two reasons. In these patients, if we postulate prevalence rates of recurrent VTE during pregnancy of 5%, the positive predictive value of compression ultrasonography would be only 10%, even if the test has a sensitivity of 96% and a specificity of 98%. Second, the timing of screening with ultrasound is problematic. Even if performed as often as weekly, a woman could still have a clinically important recurrence 2 to 3 days after a normal ultrasound. Thus, women at risk of VTE should not be screened routinely with regular noninvasive tests. Instead, we recommend that they should be investigated aggressively if symptoms suspicious of DVT or PE occur.

Recommendations (see "Summary of Recommendations" for definitions of dosing regimens)

7.2.1. For pregnant women with a single episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, we recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum (Grade 1C).

7.2.2. If the transient risk factor associated with a previous VTE event is pregnancy or estrogen related, we suggest antepartum clinical surveillance or prophylaxis (prophylactic LMWH/UFH or intermediate-dose LMWH/UFH) plus postpartum prophylaxis, rather than routine care (Grade 2C).

7.2.3. For pregnant women with a single idiopathic episode of VTE but without thrombophilia and who are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants (Grade 1C).

7.2.4. For pregnant women with thrombophilia (confirmed laboratory abnormality) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH or clinical surveillance throughout pregnancy, plus postpartum anticoagulants (Grade 1C).

7.2.5. For women with "higher risk" thrombophilias (*eg*, antithrombin deficiency, persistent positivity for the presence of APLAs, compound heterozygosity for prothrombin G20210A variant, and factor V Leiden or homozygosity for these conditions) who have had a single episode of VTE and are not receiving long-term anticoagulants, we suggest, in addition to postpartum prophylaxis, antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH, rather than clinical surveillance (Grade 2C).

7.2.6. For pregnant women with multiple (≥ 2) episodes of VTE not receiving long-term anticoagulants, we suggest antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH or prophylactic, intermediate, or adjusted-dose UFH followed by postpartum anticoagulants, rather than clinical surveillance (Grade 2C).

7.2.7. For pregnant women receiving long-term anticoagulants, we recommend LMWH or UFH throughout pregnancy (either adjusted-dose LMWH or UFH, 75% of adjusted-dose LMWH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum (Grade 1C).

7.2.8. For all pregnant women with previous DVT, we suggest the use of graduated elastic compression stockings both antepartum and postpartum (Grade 2C).

Underlying values and preferences: This recommendation places a high value on uncertain incremental benefit with stockings, and a low value on avoiding discomfort and inconvenience.

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

Collectively, congenital thrombophilias are present in at least 15% of the population and approximately 50% of gestational VTE are associated with heritable thrombophilia.[126,127] The majority of studies that have examined the risk of VTE in pregnancy have focused on these heritable thrombophilic mutations and, as a result, the risk of pregnancy-related VTE with acquired thrombophilic abnormalities remains unclear.

8.1 Risk of Pregnancy-Related VTE in Women With Thrombophilia

A number of studies have examined the relationship between hereditary thrombophilias and pregnancy-related VTE. However, methodologic limitations have made it difficult to obtain an accurate assessment these risks. In recent systematic review of nine studies that assessed the risk of VTE in pregnant women with heritable thrombophilias, all congenital thrombophilias with the exception of homozygosity for the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T) were found to be associated with a statistically significant increase in the risk of pregnancy-related VTE.[128] The highest risks were associated with homozygosity for factor V Leiden (OR, 34.40; 95% CI, 9.86–120.05) and for homozygosity of the prothrombin G20210A variant (OR, 26.36; 95% CI, 1.24–559.20). The most common inherited thrombophilias were associated with lower risks (heterozygosity for factor V Leiden: OR, 8.32; 95% CI, 5.44–12.70; and heterozygosity for the prothrombin G20210A variant: OR, 6.80; 95% CI, 2.46–18.77). Deficiencies of the endogenous antico-

agulants were also associated with moderate risk increases (antithrombin deficiency: OR, 4.69; 95% CI, 1.30–16.96; protein C deficiency: OR, 4.76; 95% CI, 2.15–10.57; protein S deficiency: OR, 3.19; 95% CI, 1.48–6.88). In a subsequently published meta-analysis undertaken to provide an accurate 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, 4.84–12.63). However, the results from cohort studies, which are likely to be more reliable, showed a lower pooled OR of 4.46 (95% CI, 1.82–10.94).[129]

Given a background incidence of VTE during pregnancy of approximately 1/1,000 deliveries, it is clear that the absolute risk of VTE in women without a prior event remains modest for those who have the most common inherited thrombophilias (heterozygosity for factor V Leiden or prothrombin G20210A variant). Consistent with this, Dizon-Townson and colleagues reported no venous thromboembolic events among members of a prospectively followed cohort of 134 factor V Leiden mutation carriers with a singleton pregnancy and no prior history of VTE (0%, 95% CI, 0–2.7%).[130] In other cohort studies, the absolute risk of pregnancy-associated VTE has been reported to range from 9 to 16% in homozygotes for the factor V Leiden mutation.[130–136] Double heterozygosity for factor V Leiden and prothrombin G20210A variant has been reported to have an absolute risk of pregnancy-associated VTE of 4.0% (95% C1, 1.4 to 16.9%).[133] A similar frequency of pregnancy-related VTE of 4.1% was reported in a retrospective cohort study of 60 women with at least one pregnancy and antithrombin, protein C or protein S deficiency.[137]

In a study of 119 women with gestational VTE and 233 controls, Gerhardt et al[138] were also able to provide a positive predictive value for each thrombophilia, assuming an underlying rate of VTE of 0.66/1,000 pregnancies, consistent with estimates from Western populations.[127] These values were 1:500 for individuals heterozygous for the factor V Leiden mutation, 1:200 for those heterozygous for the prothrombin G20210A variant and 4.6:100 for double heterozygotes. In a similar analysis of a retrospective study of 72,000 pregnancies in which women with venous thrombosis were assessed for thrombophilia and the underlying prevalence of these defects in the population was known, the risk of thrombosis was 1:437 for women with the factor V Leiden mutation, 1:113 for those with protein C deficiency, 1:2.8 for women with type 1 antithrombin deficiency and 1:42 for those with type 2 antithrombin deficiency.[139] These data suggest that women with antithrombin deficiency or homozygosity for the factor V Leiden mutation, as well as double heterozygotes, should be managed more aggressively than those with other heritable thrombophilias, especially in symptomatic kindreds.

Acquired thrombophilias have been less well studied, but persistent APLAs (lupus anticoagulants [nonspecific inhibitors] or anticardiolipin antibodies) are likely associated with an increased risk of pregnancy-related VTE.[140] Women with APLAs and no previous venous thrombosis should probably still be considered to have an increased risk of VTE and should be managed either with careful clinical surveillance for VTE or prophylactic UFH or LMWH antepartum, in addition to postpartum anticoagulants.

Hyperhomocysteinemia is associated with an increased risk of VTE in nonpregnant subjects.[141] However, it does not appear that homozygosity for MTHFR C667T, the genetic abnormality most commonly associated with hyperhomocysteinemia, is linked to an increased risk of VTE in pregnant women.[128] As clinical events in homozygotes are likely to reflect the interaction of the genotype with a relative deficiency of vitamins such as B_{12} and folic acid, the absence of an association of this genotype with gestational VTE may reflect pregnancy-related physiologic reduction in homocysteine levels and/or the effects of folic acid supplements that are now taken widely by women in pregnancy for prevention of neural tube defects.[142]

Recommendation

8.1.1. For pregnant patients with thrombophilia but no prior VTE, we recommend that physicians do not use routine pharmacologic antepartum prophylaxis but instead perform an individualized risk assessment (Grade 1C)**.**

8.2 Prevention of Pregnancy-Related VTE in Women With Thrombophilia

The management of pregnant women with known thrombophilia and no prior VTE remains controversial because of our limited knowledge of the natural histories of various thrombophilias and a lack of trials of VTE prophylaxis. There continues to be a paucity of high-quality data measuring the effectiveness and safety of antithrombotic agents in preventing VTE in pregnant women with thrombophilia and no prior history of DVT or PE. Thus, recommendations for prevention are based only on case-control studies, a small number of prospective cohort studies and generalizations from studies in nonpregnant patients. The risk of venous thromboembolism appears to

begin early in pregnancy[97]; therefore, when antepartum prophylaxis is utilized, it should be commenced in the first trimester.

Recommendations

8.2.1. For pregnant women with no prior history of VTE but antithrombin deficiency, we suggest antepartum and postpartum prophylaxis (Grade 2C)**.**

8.2.2. For all other pregnant women with thrombophilia and no prior VTE, we suggest antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants (Grade 2C)**.**

9.0 Thrombophilia and Pregnancy Complications

Adverse pregnancy outcomes are not infrequent. Twenty-five percent of human conceptions end in miscarriage. Five percent of women have two or more successive losses, and 1 to 2% have three or more consecutive losses.[143] Maternal or fetal anatomic, chromosomal, endocrinologic or immunologic problems are detected in a small number of cases of recurrent loss but, in the majority, a cause is not identified. Preeclampsia, a leading cause of both fetal and maternal morbidity and mortality, is seen in 3% to 7% of pregnancies, while placental abruption is uncommon (0.5% of gestations) but carries a high risk of fetal mortality.[144]

Successful pregnancy outcome is dependent on trophoblast invasion into the uterine vasculature and on the development and maintenance of an adequate uteroplacental circulatory system. It is hypothesized that inadequate placentation and damage to the spiral arteries with impaired flow and prothrombotic changes[145] lead to placental-medicated pregnancy complications. The low-pressure uteroplacental system, much like the venous system, may be susceptible to thrombotic complications in hypercoagulable states.[145] Thrombophilias may also magnify the maternal inflammatory response and activation of coagulation seen in response to trophoblast dysfunction in preeclampsia. Animal studies suggest that the hemostatic system plays an important role in placental and fetal development. For example, there are structural abnormalities (thinning of the layer lining the maternal lacunae, reduced number of trophoblast cellular contacts) in the placentae of tissue-factor null mice embryos[146] and anticardiolipin antibodies have been shown to inhibit trophoblast proliferation[147] and embryo implantation.[148] *In vitro* observations suggest that the presence of activated coagulation factors results in cell-type specific changes in trophoblast gene expression.[149] Annexin V, an anticoagulant phospholipids-binding protein found on normal placental villi, appears to be reduced in the presence of antiphospholipid antibodies and it has been hypothesized that this may lead to placental insufficiency and fetal loss.[150] Inactivation of the gene for protein C is associated with mice embryo death,[151] as is absence of thrombomodulin.[152]

9.1 Risk of Pregnancy Complications in Women With Thrombophilia

The most compelling data for a link between thrombophilia and pregnancy complications derives from studies in women with APLAs. In addition to the data cited above, there is convincing evidence from clinical studies that the presence of APLAs is associated with an increased risk of pregnancy loss.[128,153–156] Further, antithrombotic therapy with heparin and low-dose aspirin has been shown to improve pregnancy outcome in these women with these antibodies.[156] However, 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 (IUGR)[157–174]; with conflicting results likely the result of small sample sizes and heterogeneity of study participants.

There is substantial interest in examining whether heritable thrombophilias are also associated with adverse pregnancy outcome and whether this can be ameliorated by antithrombotic therapy. Many studies have examined the association between thrombophilia and pregnancy complications, often with differing results,[128,145] likely reflecting heterogeneity of study design, sample size, inclusion criteria, population studied, outcome definition, and thrombophilias studied. However, the results of a recent systematic review that examined 25 studies in 7,167 women confirm an association.[128]

Available data suggest that both acquired and inherited thrombophilias are associated with an increased risk of early (recurrent) fetal loss (Table 6). In particular, associations were observed with anticardiolipin antibody and lupus anticoagulant (nonspecific inhibitor) positivity, as well as homozygosity and heterozygosity for the factor V Leiden mutation and heterozygosity for the prothrombin G20210A variant.[128] Separation of early (recurrent) loss into recurrent pregnancy loss in the first trimester and single loss in the second trimester also yielded significant associations with thrombophilia. Thus, there may be a higher risk of recurrent first trimester

loss in women with the factor V Leiden mutation (OR, 1.91; 95% CI, 1.01–3.61), the prothrombin G20210A variant (OR, 2.7; 95% CI, 1.37–5.34), anticardiolipin antibodies (OR, 5.05; 95% CI, 1.82–14.01), or elevated homocysteine levels (OR, 4.21; 95% CI, 1.28–13.87). The factor V Leiden mutation (OR, 4.12; 95% CI, 1.93–8.81) and prothrombin G20210A variant (OR, 8.60; 95% CI, 2.18–33.95) were also associated with nonrecurrent second trimester loss. Other metaanalyses have reported similar associations for early pregnancy loss.[175–177] Most studies included in systematic reviews and meta-analysis are case control in design and, therefore, may overestimate the magnitude of association. The NOHA first study, a large carefully designed case-control study nested in a cohort of nearly 32,700 women, of whom 18% had pregnancy loss with first gestation,[178] found on multivariate analysis a clear association between unexplained first pregnancy loss between 10 weeks and 39 weeks gestation and heterozygotes for factor V Leiden (OR, 3.46; 95% CI, 2.53–4.72) and prothrombin gene mutations (OR, 2.60; 95% CI, 1.86–3.64); although no association was observed in losses prior to 10 weeks. However, in a nested carrier control analysis of a prospective cohort study of 4,885 pregnant women (134 with the factor V Leiden mutation) published at approximately the same time, maternal carriage of the factor V Leiden mutation was not associated with increased pregnancy loss, preeclampsia, placental abruption or small for gestational age births.[130]

Late unexplained fetal loss has also been associated with maternal thrombophilia, although results of case control studies have again been inconsistent with some reporting an association and others identifying no association with thrombophilia.[128,179,180] However, on systematic review,[128] the OR was 2.06 (95% CI, 1.10–3.86) for heterozygosity for the factor V Leiden mutation and 2.66 (95% CI, 1.28–5.53) for heterozygosity for the prothrombin gene mutation. The strongest association for late fetal loss was seen in women with protein S deficiency (OR, 20.9; 95% CI, 3.70–109.15).[128]

Since the first reports of an association between preeclampsia and inherited thrombophilia in 1995,[181] a number of case-control and cohort studies have investigated this association. Although the results from individual studies are variable, a meta-analysis of 25 studies with 11,183 women[128] found significant associations with factor V Leiden and prothrombin G20210A variant heterozygosity, MTHFR C677T variant homozygosity, anticardiolipin antibody positivity, and hyperhomocysteinemia (Table 7). Overall, the increase in risk of preeclampsia with thrombophilia appears modest. It has been suggested that thrombophilia acts by contributing to the severity of disease expression once the condition arises.[182–184]

Several studies have described an association between placental abruption and thrombophilia and, on metaanalysis,[128] significant associations were reported in women heterozygous for the prothrombin G20210A variant, as well as those heterozygous for the factor V Leiden mutation (Table 8) only. The association between IUGR and thrombophilia remains controversial. As shown in Table 9, metaanalysis of five studies (n = 195 women), demonstrated a significant association between anticardiolipin antibody positivity and IUGR. Although there was a trend toward an increased risk of IUGR in women with congenital thrombophilia, but no statistically significant associations were found.[128]

Given the uncertainty associated with the magnitude of risk, the uncertainty associated with any benefits of prophylaxis in women with heritable thrombophilia (outlined below), and the uncertainty about the effect on anxiety and well-being in women screened vs not screened, whether screening for congenital thrombophilias is in the best interests of women with pregnancy complications remains uncertain.

Table 7—*Risk of Preeclampsia in Women With Thrombophilia (Section 9.1)**

Type of Thrombophilia	Thrombophilia	No Thrombophilia	OR (95% CI)
Factor V Leiden (homozygous)	4/5	608/1,143	1.87 (0.44–7.88)
Factor V Leiden (heterozygous)	161/249	1,790/3,673	2.19 (1.46–3.27)
Prothrombin gene mutation (heterozygous)	42/71	937/2,028	2.54 (1.52–4.23)
MTHFR C677T (homozygous)	221/481	1,234/3,205	1.37 (1.07–1.76)
Antithrombin deficiency	1/1	57/131	3.89 (0.16–97.19)
Protein C deficiency	3/3	60/104	5.15 (0.26–102.22)
Protein S deficiency	14/20	158/402	2.83 (0.76–10.57)
Anticardiolipin antibodies	130/217	803/2,428	2.73 (1.65–4.51)
Lupus anticoagulants (nonspecific inhibitor)	63/89	426/981	1.45 (0.70–4.61)
Hyperhomocysteinaemia	37/41	257/364	3.49 (1.21–10.11)

*Data are presented as No./total. Data derived from Robertson et al.[128]

Table 8—*Risk of Placental Abruption in Women With Thrombophilia (Section 9.1)

Type of Thrombophilia	Thrombophilia	No Thrombophilia	OR (95% CI)
Factor V Leiden (homozygous)	3/3	24/53	8.43 (0.41–171.20)
Factor V Leiden (heterozygous)	13/28	64/332	4.70 (1.13–19.59)
Prothrombin gene mutation (heterozygous)	10/20	44/400	7.71 (3.01–19.76)
MTHFR C677T (homozygous)	3/14	401/183	1.47 (0.40–5.35)
Antithrombin deficiency	1/2	26/54	1.08 (0.06–18.12)
Protein C deficiency	1/1	22/66	5.93 (0.23–151.58)
Protein S deficiency	4/8	19/59	2.11 (0.47–9.34)
Anticardiolipin antibodies	6/12	44/111	1.42 (0.42–4.77)
Hyperhomocysteinaemia	32/42	96/195	2.40 (0.36–15.89)

*Data are presented as No./total. Data derived from Robertson et al.[128]

Recommendations

9.1.1. For women with recurrent early pregnancy loss (three or more miscarriages), we recommend screening for APLAs (Grade 1A).
9.1.2. For women with severe or recurrent preeclampsia or IUGR, we suggest screening for APLAs (Grade 2C).

9.2 Prevention of Pregnancy Complications in Women With Thrombophilia

In view of the data showing an association between thrombophilia and adverse pregnancy outcomes, clinicians are increasingly using antithrombotic therapy in women at risk of these complications (Tables 10–12).[185–206] The combination of UFH and low-dose aspirin has been shown to be effective in reducing miscarriage rates in women with APLA syndrome with prior recurrent fetal loss.[156,185–187] Of the interventions examined in a recent systematic review[156] that summarized the data from 13 randomized or quasirandomized trials including a total of 849 pregnant women with APLA and a history of pregnancy loss, only UFH combined with aspirin (two trials; n = 150) was shown to reduce the incidence of pregnancy loss (RR, 0.46; 95% CI, 0.29–0.71 when compared with aspirin alone).[185,186] The use of higher dose UFH and aspirin did not decrease the risk of pregnancy loss compared with low UFH and aspirin (one trial; n = 50).[156,188] On its own, aspirin (three trials, n = 135) demonstrated no significant reduction in pregnancy loss compared with usual care[189] or placebo[190,191] (RR, 1.05; 95% CI, 0.66–1.68).[156] The combination of LMWH with aspirin had no statistically significant effect on pregnancy loss when compared with aspirin alone (R,R 0.78; 95% CI, 0.39–1.57)[156,193] or with IV gamma globulin (RR, 0.37; 95% CI, 0.12–1.16)[156,194]; although in both case, the point estimate was in the direction of benefit.[156] Patients enrolled in the study comparing LMWH and aspirin with aspirin alone[193] may have been at relatively low risk of recurrent loss (low APLA titers) and, thus, less likely to show benefit with the addition of LMWH. This study has also been criticized because 24% of patients crossed over to the other treatment arm; however, the results were similar between adherent and nonadherent patient groups.[193] No study comparing LMWH and UFH was included in this systematic review and the relative effectiveness of UFH vs LMWH with respect to prevention of recurrent pregnancy loss in women with APLA is not established. However, if the effect of UFH on prevention of recurrent loss is mediated by its antithrombotic properties, then LMWH should be equally effective. Consistent with this, the results of two recent pilot studies suggest that the combination of LMWH and aspirin might be equivalent to UFH and aspirin in preventing recurrent pregnancy loss.[195,196]

The data surrounding the use of antithrombotic therapy in women with hereditable thrombophilia and pregnancy loss is less convincing and consists of

Table 9—*Risk of IUGR in Women With Thrombophilia (Section 9.2)

Type of Thrombophilia	Thrombophilia	No Thrombophilia	OR (95% CI)
Factor V Leiden (homozygous)	1/1	60/153	4.64 (0.19–115.68)
Factor V Leiden (heterozygous)	25/49	512/1147	2.68 (0.59–12.13)
Prothrombin gene mutation (heterozygous)	25/44	583/1375	2.92 (0.62–13.70)
MTHFR C677T (homozygous)	62/121	460/961	1.24 (0.84–1.82)
Anticardiolipin antibodies	7/60	15/800	6.91 (2.70–17.68)

*Data are presented as No./total. Data derived from Robertson et al.[128]

Table 10—*Randomized Trials and Prospective Cohort Studies of the Prevention of Complications in Pregnant Women With Thrombophilia: Clinical Description and Results (Section 9.2)***

Study/Yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Fetal Loss, No./Total (%)	IUGR, No./Total (%)	Preeclampsia, No./Total (%)	Placental Abruption, No./Total (%)	Maternal Bleeding	Comments
Thrombophilia: APLA									
Cowchock and Reece[189]/1997	Aspirin 81 mg/d Usual care	Aspirin†: 11 (100.0) Usual: 8 (100.0)	Pregnancy loss or delivery	Aspirin: 1/11 (9.1) Usual: 0/8 RR: 2.25 95% CI: 0.10–49.04	Aspirin: 0/10 Usual: 1/8 (12.5) RR: 0.27 95% CI: 0.01–5.92	NR	NR	NR	
Tulppala et al[191]/1997	Aspirin 50 mg/d Placebo	Aspirin†: 5/6 (83.3) Placebo: 6 (50.0)	Pregnancy loss or delivery	Aspirin: 4/5 (80.0) Placebo: 2/3 (66.7) RR 1.20 95% CI: 0.48–2.99	NR	NR	NR	NR	
Pattison et al[190]/2000	Aspirin 75 mg/d Placebo	Aspirin†: 20/25 (80.0) Placebo: 20/25 (80.0)	Pregnancy loss or delivery	Aspirin: 4/20 (20.0) Placebo: 3/20 (15.0) RR: 1.33 95% CI: 0.34–5.21	Aspirin: 1/16 (6.2) Placebo: 4/17 (23.5) RR: 0.27 95% CI: 0.03–2.13	Aspirin: 3/20 (15.0) Placebo: 3/20 (15.0) RR: 1.00 95% CI: 0.23–4.37	NR	Aspirin: 9/20 (45.0) Placebo: 7/20 (35.0) RR: 1.29 95% CI: 0.6–2.72	All bleeding events minor
Laskin et al[192]/1997	Prednisone (0.8 mg/kg/d for 4 wk (maximum 60 mg) followed by 0.5 mg/kg/d (maximum 40 mg) and aspirin (100 mg/d until wk 36 or shortly before delivery) Placebo	Prednisone plus aspirin†: 101/101 Placebo: 101/101	2 yr postpartum	Prednisone plus aspirin: 35/101 (34.6) Placebo: 44/101 (43.6) RR: 0.80 95% CI: 0.56–1.13	Prednisone plus aspirin: 17/61 (27.9) two twin pairs Placebo: 11/61 (18.0) six twin pairs RR: 1.55 95% CI: 0.79–3.20	NR	NR	NR	
Rai et al[186]/1997	Aspirin 75 mg/d UFH 5,000 U SC bid plus aspirin 75 mg/d	Aspirin: 45/45 UFH plus aspirin†: 45/45	Pregnancy loss or delivery	Aspirin: 26/45 (57.8) UFH plus aspirin: 13/45 (28.9) [p = 0.01] RR: 0.50 95% CI: 0.30–0.84	Aspirin: 1/19 (5.3) UFH plus aspirin: 3/32 (9.4) RR: 1.78 95% CI: 0.20–15.93	Aspirin: 1/45 (2.2) UFH plus aspirin: 0/45 (0.0) RR: 0.33 95% CI: 0.01–7.92	NR	NR	
Kutteh[185]/1996	Aspirin 81 mg/d UFH 5,000 U SC bid adjusted to attain 6-h post injection aPTT at 1.2–1.5 times baseline plus aspirin 81 mg/d	Aspirin: 25/25 UFH plus aspirin†: 25/25	Pregnancy loss or delivery	Aspirin: 14/25 (56.0) UFH plus aspirin: 5/25 (20.0) RR: 0.36 95% CI: 0.15–0.84	Aspirin: 1/11 (9.1) UFH plus aspirin: 3/20 (15.0) RR: 1.65 95% CI: 0.19–14.03	Aspirin: 1/11 (9.1) UFH plus aspirin: 2/20 (10.0) RR: 1.10 95% CI: 0.11–10.81	NR	Aspirin: 1/11 (9.1) UFH plus aspirin: = 3/20 (15.0) RR: 1.65 95% CI: 0.19–14.03	All bleeding events considered minor
Kutteh and Ermel[188]/1996	UFH 5,000 U SC bid adjusted to maintain aPTT at 1.2–1.5 times baseline (higher dose) plus aspirin 81 mg/d UFH 5,000 U SC bid adjusted to maintain aPTT at upper limit of normal (lower dose) plus Aspirin 81 mg/d	UFH higher dose plus aspirin: 25/25 UFH lower dose plus aspirin†: 25/25	Pregnancy loss or delivery	UFH higher dose plus aspirin: 5/25 (20.0) UFH lower dose plus aspirin: 6/25 (24.0) RR: 0.83 95% CI: 0.29–2.38	NR	NR	NR	NR	

Table 10—*Continued*

Study/Yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Fetal Loss, No./Total (%)	IUGR, No./Total (%)	Preeclampsia, No./Total (%)	Placental Abruption, No./Total (%)	Maternal Bleeding	Comments
Franklin and Kutteh[187]/ 2002	Group 1 (NS or ACA PC or ACA PS): aspirin 81 mg daily plus prenatal vitamins plus UFH 5000 U SC bid if patient ≤ 150 lb or 6,000 U SC bid if > 150 lb	Group 1†: 25/25	Pregnancy loss or delivery	Group 1: 6/25 (24.0) RR: 0.45 95% CI: 0.20–0.98	Group 1: 2/19 (10.5) RR: 1.26 95% CI: 0.13–12.46	Group 1: 2/19 (10.5) RR: 2.40 95% CI: 0.25–22.75		Group 1: 3/19 (15.8) RR: 0.95 95% CI: 0.18–4.87	All bleeding events considered minor
	Group 2 (ACA PI or ACA PG or ACA PE): aspirin 81 mg/d plus prenatal vitamins plus heparin 5,000 U SC bid if patient ≤ 150 lb or 6,000 U SC bid if > 150 lb	Group 2†: 28/28		Group 2: 10/28 (35.7) RR: 0.66 95% CI: 0.36–1.22	Group 2: 1/18 (5.5) RR: 0.67 95% CI: 0.05–9.66	Group 2: 0/18 RR: 0.23 95% CI: 0.01–5.18		Group 2: 2/18 (11.1) RR: 0.67 95% CI: 0.11–4.11	
	Group 3 (ACA PI or ACA PG or ACA PE): aspirin 81 mg/d	Group 3: 26/26 Note: No. recruited not reported		Group 3: 4/26 (53.8)	Group 3: 1/12 (8.3)	Group 3: 1/12 (8.3)		Group 3: 2/12 (16.7)	
Triolo et al[194]/2003	IVIG 400 mg/kg/d given for 2 consecutive d followed by a single dose each month LMWH 5,700 IU/d SC plus aspirin 75 mg/d	IVIG: 21/21 (100.0) LMWH plus aspirin†: 19/21 (90.5)	Pregnancy loss or delivery	IVIG = 9/21 (42.9) LMWH plus aspirin: 3/19 (15.7) [p = 0.06] RR: 0.37 95% CI: 0.12–1.16	NR	NR	NR	NR	
Farquharson et al[193]/2002	Aspirin 75 mg/d LMWH 5,000 U/d SC until delivery plus aspirin 75 mg/d	Aspirin: 47/47 (100.0) LMWH plus Aspirin†: 51/51 (100.0)	Pregnancy loss or delivery	Aspirin: 13/47 (27.6) LMWH plus aspirin: 11/51 (21.6) RR: 0.78 95% CI: 0.39–1.57	NR	NR	NR	NR	
Stephenson et al[196]/2004	Aspirin 81 mg/d starting prior to conception plus LMWH (luteal phase or first timester dalteparin 2,500 IU SC qd; second trimester: dalteparin 5,000 IU SC qd; third trimester: dalteparin 7,500 IU SC qd) Aspirin 81 mg/d starting prior to conception plus UFH (luteal phase or first trimester: 5,000 U SC bid; second trimester: 7,500 U SC	bid; third trimester: 10,000 U SC bid)	LMWH plus aspirin†: 14/14 (100.0) UFH plus aspirin: 14/14 (100.0)	Pregnancy loss or delivery	LMWH plus aspirin: 4/13 (30.7) UFH plus aspirin: 9/13 (69.2) RR: 0.44 95% CI: 0.18–1.08	NR	LMWH plus aspirin: 1/13 (7.8) UFH plus aspirin: 0/13 (0.0) RR: 3.00 95% CI: 0.13–67.52	NR	NR
Noble et al[195]/2005	Aspirin 81 mg/d starting prior to conception plus LMWH (enoxaparin 40 mg/d SC) Aspirin 81 mg/d starting prior to conception plus UFH (5,000 to 6,000 U SC bid depending upon weight)	LMWH plus aspirin†: 25/25 (100.0) UFH plus aspirin: 25/25 (100.0)	2 wk after delivery	LMWH + aspirin: 4/25 (16.0) UFH plus aspirin: 5/25 (20.0) RR: 0.80 95% CI: 0.24–2.64	LMWH plus aspirin: 1/21 (4.8) UFH plus aspirin: 1/20 (5.0) RR: 0.95 95% CI: 0.06–14.22	LMWH +4 aspirin: 0/25 (0.0) UFH plus aspirin: 0/25 (0.0) RR: 1.00 95% CI: 0.02–48.53	NR	LMWH plus aspirin: 3/25 (12.0) UFH plus aspirin: 2/25 (5.0) RR: 1.5 95% CI: (0.27–8.22)	All bleeding events classified as minor

Table 10—*Continued*

Study/yr	Interventions	Patients Analyzed, No./Total (%)	Length of Follow-up	Fetal Loss, No./Total (%)	IUGR, No./Total (%)	Preeclampsia, No./Total (%)	Placental Abruption, No./Total (%)	Maternal Bleeding	Comments
Hereditary thrombophilia									
Kupferminc et al[200]/2001	LMWH (enoxaparin 40 mg/d SC) plus aspirin 100 mg/d	33/33	Pregnancy loss or delivery	0.33 (0.0)	2/33 (6.1)	1/33 (3.0)	0/33 (0.0)	0/33 (0.0)	
Brenner et al[198]/2000	LMWH (enoxaparin 40 mg/d SC if one thrombophilia or 80 mg/d SC if two thrombophilas) Aspirin 75 mg/d was added if APLA	50/50	4 wk after delivery	15/61 gestations (76.2)	NR	NR	NR	1/61 (1.6)	All bleeding events classified as minor
Carp et al[199]/2003	LMWH (enoxaparin 40 mg/d SC) Retrospective control (no prophylaxis)	LMWH†: 37/37 (100.0) Control: 48/48 (100.0))	Pregnancy loss or delivery	LMWH: 11/37 (29.7) Control: 27/48 (56.3) RR: 1.89 95% CI: 1.09–3.29	NR	LMWH: 2/26 (7.6) Control: 1/26 (3.8) RR: 2.00 95% CI: 0.19–20.72	NR	NR	
Tzafettas et al[206]/2005	LMWH (nadroparin 0.3 mL bid SC) plus aspirin 80 mg	Thrombophlilia†: 24/24 (100.0) No thrombophilia: 27/27 (100.0)	3 mo postpartum	Thrombophilia: 4/24 (16.6) No thrombophilia: 4/27 (14.8) p = not significant RR: 1.13 95% CI: 0.32–4.01	Thrombophilia: 6/20 (30.0) No thrombophilia: 4/23 (17.4) RR: 1.73 95% CI: 0.57–5.26	Thrombophilia: 6/24 (25.0) No thrombophilia: 2/27 (7.4) RR: 3.38 95% CI: 0.75–15.17	Thrombophilia: 2/24 (8.3) No thrombophilia: 0/27 (0.0) RR: 5.60 95% CI: 0.28–111.15	NR	
Gris et al[205]/ 2004	Aspirin 100 mg/d and folic acid 5 mg/d LMWH (enoxaparin 40 mg/d SC) and folic acid 5 mg/d	Aspirin: 80/80(100.0) LMWH†: 80/80(100.0)	Pregnancy loss or delivery	Aspirin: 57/80 (71.2) LMWH: 11/80 (13.7) p < 0.0001 RR: 0.19 95% CI: 0.11–0.34	Aspirin: 7/23 (30.4) LMWH: 7/71 (9.9) RR: 0.32 95% CI: 0.13–0.83	Aspirin: 3/80 (3.8) LMWH: 4/80 (5.0) RR: 1.33 95% CI: 4.77–0.69	NR	NR	
Brenner et al[201]/ 2005, Brenner et al[202]/2005	40 mg/d enoxaparin SC 80 mg/d enoxaparin SC	Enoxaparin 40 mg/d: 83/89 (93.3) Enoxaparin 80 mg/d†: 83/91 (91.2)	6 wk postpartum	Enoxaparin 40 mg/d: 19/89 (21.3) Enoxaparin 80 mg/d: 26/91 (28.6) RR: 1.34 95% CI: 0.80–2.24	Enoxaparin 40 mg/d: 7/65 (10.8) Enoxaparin 80 mg/d 5/63 (7.9) RR: 0.74 95% CI: 0.25–2.20	Enoxaparin 40 mg/d: 3/89 (3.4) Enoxaparin 80 mg/d: 4/91 (4.4) p = 0.72 RR: 1.30 95% CI: 0.30–5.66	Enoxaparin 40 mg/d: 4/89 (4.5) Enoxaparin 80 mg/d 3/91 (3.3) p = 0.68 RR: 0.73 95% CI: 0.17–3.18	Enoxaparin 40 mg/d: 0/89 (0.0) Enoxaparin 80 mg/d 0/91 (0.0) RR: 1.02 95% CI: 0.02–50.97	

*The methodologic quality description portion of the table can be found in the online version of this article as a data supplement.
†Identified as experimental arm for RR calculation.

predominantly of small uncontrolled trials or observational studies (Tables 10, 12).[197–202,205,206] In an early study, administration of LMWH (enoxaparin 20 mg/d) to 20 women with primary early recurrent fetal loss and impaired fibrinolytic capacity resulted in normalization of fibrinolysis. Sixteen of the study participants conceived and a live birth occurred in 13 (81%).[197] A recent systematic review described outcomes in 2,215 pregnancies treated with LMWH,[70] including 370 pregnancies with a history of recurrent pregnancy loss. Of these, 85.4% had successful outcome. Prospective cohort studies of pregnant women with hereditary thrombophilia with recurrent pregnancy losses have reported an increase in the frequency of live births with LMWH compared to a previous untreated pregnancy[198] or concurrent untreated patients.[199] In the LIVE-ENOX trial, in which women with hereditary thrombophilia and recurrent pregnancy loss were randomized to one of two doses of enoxaparin (40 mg/d and 80 mg/d), there was no significant difference in pregnancy outcomes between the two groups; however, the rate of live birth was higher than might have been expected given the histories.[201,202] There has been considerable debate about this trial[203,204] focusing on its limitations, particularly the absence of an untreated control group, the heterogeneous entry criteria and the risk of regression toward the mean with the use of a historical comparison group. Recently, Gris et al[205] reported that treatment with 40 mg of enoxaparin daily in women with a thrombophilia (factor V Leiden, prothrombin gene mutation or protein S deficiency) and one previous pregnancy loss after 10 weeks of gestation, resulted in a significantly higher live birth rate (86%) compared with low-dose aspirin alone (29%). However, this trial also has significant limitations including small sample size, absence of an untreated control group, and inadequate concealment of allocation. Further, given that the success rate of subsequent pregnancies is relatively high after a single miscarriage, it is difficult to assess the implications of these results.

The data described above provide some circumstantial evidence that LMWH may improve the pregnancy outcome in women with heritable thrombophilia and recurrent pregnancy loss or loss after 10 weeks; however, available studies have important methodologic limitations and firm recommendations cannot be made regarding the use of antithrombotic therapy in this patient population. Treatment that prevents fetal loss may not prevent other complications and, at present, there are insufficient data on the effect of antithrombotic interventions in other adverse pregnant outcomes in women with thrombophilia to provide any recommendations.

Recommendation

9.2.1. For women with APLAs and recurrent (three or more) pregnancy loss or late pregnancy loss and no history of venous or arterial thrombosis, we recommend antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin (Grade 1B)**.**

10.0 Management of Women With a History of Preeclampsia and No Thrombophilia

Preeclampsia is associated with microvascular fibrin deposition indicative of activation of platelets and coagulation,[207] as well as widespread endothelial dysfunction.[208–211] The manifestations of this disease are protean[212] and preeclampsia should not be thought of as a single disease entity, but rather a maternal response to abnormal placentation. This response is influenced by the maternal phenotype and patients with essential hypertension, diabetes mellitus, underlying renal disease, high body mass index ($\geq$ 35 kg/m^2), increased age ($\geq$ 35 years), and prior preeclampsia are at increased risk.[213,214] As discussed above, women with a thrombophilic disorder, whether it be acquired or heritable, are also more likely to have preeclampsia. Although thrombophilia is not the cause of preeclampsia, it may contribute to the expression of the disease. Indeed, in their systematic review, Morrison and colleagues[184] found an association with disease severity, rather than disease occurrence.

10.1 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. In large systematic reviews, the use of antiplatelet agents (primarily low-dose aspirin) has been associated with modest reductions (in the range of 15% to 20%) in the relative risk of preeclampsia (OR, 0.86; 95% CI, 0.76–0.96[23] and RR, 0.81; 95% CI, 0.75–0.81[215]). Statistically significant reductions in other outcomes such as fetal or neonatal death (RR, 0.84, 95% CI, 0.74–0.96; number needed to treat, 227; 95% CI, 128–909) have also been reported.[215] Overall, approximately 68 women (95% CI, 50–109) would need to be treated to prevent one case of preclampsia.[215] For high-risk women, the number needed to treat drops to 18 (95% CI, 13–30), while that for moderate risk women is 188 (95% CI, 74–303).[215]

Some have suggested anticoagulant therapy with

Table 11—*Randomized Trials and Prospective Cohort Studies of the Prevention of Complications in Pregnant Women With Thrombophilia (APLA): Summary Evidence Profile (Section 9.2)*

Quality Assessment								Summary of Findings				
								Treatment		Effect		
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Aspirin, No./Total (%)	Placebo, No./Total (%)	RR (95% CI)	Events Prevented per 1,000 Treated	Quality
Aspirin vs placebo or usual care												
Fetal loss												
3*	RCT	Some limitations†	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	9/36 (25.0)	5/31 (16.1)	1.28 (0.61–2.68)	Not§ significant	Low
IUGR												
2‖	RCT	Some limitations†	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	1/26 (3.8)	5/25 (20.0)	0.27 (0.05–1.50)	Not§ significant	Low
Preeclampsia												
1¶	RCT	Some limitations†	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	3/20 (15.0)	3/20 (15.0)	1.00 (0.23–4.37)	Not§ significant	Low
Maternal bleeding												
1¶	RCT	Some limitations†	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	9/20 (45.0)	7/20 (35.0)	1.29 (0.60–2.77)	Not§ significant	Low
Prednisone plus aspirin vs placebo												
Fetal loss												
1#	RCT	No serious limitations	No important inconsistency	No problems	No imprecision	No reporting bias	No strong association	35/101 (34.6)	44/101 (43.6)	0.80 (0.56–1.13)	87 per 1,000	High
IUGR												
1#	RCT	No serious limitations	No important inconsistency	No problems	Some** imprecision	No reporting bias	No strong association	17/61 (27.9)	11/61 (18.0)	1.55 (0.79–3.20)	Not significant§	Moderate
UFH plus aspirin vs aspirin												
Fetal loss												
3‡‡	RCT‖‖ cohort	Some† limitations	No important inconsistency	No problems	No imprecision	No reporting bias	Strong Association	34/123 (27.6)	54/96 (56.3)	0.50 (0.35–0.70)	281 per 1,000	Moderate
IUGR												
3‡‡	RCT‖‖ coohort	Some† limitations	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	9/89 (10.1)	3/42 (7.1)	1.42 (0.41–4.95)	Not§ significant	Low
Preeclampsia												
3‡‡	RCT‖‖ cohort	Some† limitations	No important inconsistency	No problems	Large*** imprecision (−2)	No reporting bias	No strong association	4/102 (3.9)	3/68 (4.4)	0.70 (0.16–2.96)	Not§ significant	Low
Maternal bleeding												
2†††	Cohort	Some† limitations	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	8/57 (14.0)	3/23 (13.0)	1.03 (0.30–3.51)	Not§ significant	Low
Aspirin plus UFH (high dose) vs aspirin plus UFH (low dose)												
Fetal loss												
1†††	Cohort	Some† limitations	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	5/25 (20.0)	6/25 (24.0)	0.83 (0.29–2.38)	Not§ significant	Low
IVIG vs LMWH plus aspirin												
Fetal loss												
1‡‡‡	RCT	Some† limitations	No important inconsistency	No problems	Large‡ imprecision (−2)	No reporting bias	No strong association	9/21 (42.9)	3/19 (15.8)	2.71 (0.86–8.57)	Not§ significant	Low
Aspirin vs LMWH plus aspirin												
Fetal loss												
1§§	RCT	Some† limitations	No important inconsistency	No problems	Some** imprecision	No reporting bias	No strong association	13/47 (21.6)	11/51 (27.7)	1.28 (0.64–2.58)	Not§ significant	Low

Table 11—*Continued*

Quality Assessment								Summary of Findings				
								Treatment		Effect		
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Aspirin, No./Total (%)	Placebo, No./Total (%)	RR (95% CI)	Events Prevented per 1,000 Treated	Quality
Aspirin plus LMWH vs aspirin plus UFH												
Fetal loss												
2‖‖‖	RCT and cohort	Some† limitations	No important inconsistency	No problems	No imprecision	No reporting bias	No strong association	8/38 (21.1)	14/38 (36.8)	0.55 (0.27–1.12)	166 per 1,000	Moderate
IUGR												
1###	Cohort	Some† limitations	No important inconsistency	No problems	Large*** imprecision (−2)	No reporting bias	No strong association	1/21 (4.8)	1/20 (5.0)	0.95 (0.06–14.22)	Not§ significant	Low
Preeclampsia												
2‖‖‖	RCT and cohort	Some† limitations	No important inconsistency	No problems	Large*** imprecision (−2)	No reporting bias	No strong association	1/38 (2.6)	0/38 (0)	3.00 (0.13–67.51)	Not§ significant	Low
Maternal bleeding												
1###	Cohort	Some† limitations	No important inconsistency	No problems	Large*** imprecision (−2)	No reporting bias	No strong association	3/25 (12.0)	2/25 (8.0)	1.50 (0.27–8.22)	Not§ significant	Low

*Includes Cowchock and Reece[189]/1997, Tulppala et al[191]/1997, and Pattison et al[190]/2000.
†Some methodological limitations; see Methods Table in online supplemental material.
‡95% CI includes no effect and < 20 events.
§95% CI includes no effect. Events per 1,000 treated not calculated.
‖Includes Cowchock and Reece[189]/1997 and Pattison et al[190]/2000.
¶Includes Pattison et al[190]/2000.
#Includes Laskin et al[192]/1997.
**95% CI includes no effect.
‡‡Includes Rai et al[186]/1997, Franklin and Kutteh[187]/2002, and Kutteh[185]/1996.
§§Includes Farquharson et al[193]/2002.
‖‖‖One study is an RCT, and two studies are prospective cohort studies.
***95% CI includes no effect and < 10 events.
†††Includes Franklin and Kutteh[187]/2002 and Kutteh[185]/1996.
‡‡‡Includes Kutteh and Ermel[188]/1996.
§§§Includes Triolo et al[194]/2003.
‖‖‖‖Includes Stephenson et al[196]/2004 and Noble et al[195]/2005.
###Includes Noble et al[195]/2005.

Table 12—*Randomized Trials and Prospective Cohort Studies of the Prevention of Complications in Pregnant Women With Thrombophilia (Hereditary Thrombophilia): Summary Evidence Profile (Section 9.2)*

Quality Assessment							Summary of Findings				
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Treatment, No./Total (%)	Effect, RR (95% CI)	Events Prevented per 1,000 Treated	Quality
Aspirin plus LMWH											
Fetal loss											
3*	Cohort	No serious limitations	Some† inconsistency	No problems	Some‡ imprecision	None	Not available	19/118 (16.1)	Pooled proportion§, 0.118 (0.006–0.341)		Low
IUGR											
2*	Cohort	No serious limitations	No important inconsistency	No problems	Some‡ imprecision	None	Not available	8/53 (15.1)	Pooled proportion,§ 0.169 (0.01–0.449)		Low
Preeclampsia											
2*	Cohort	No serious limitations	No important inconsistency	No problems	Some‡ imprecision	None	Not available	7/57 (12.3)	Pooled proportion,§ 0.129 (0.002–0.402)		Low
Placental abrubtion											
2*	Cohort	No serious limitations	No important inconsistency	No problems	Some‡ imprecision	None	Not available	2/57 (3.5)	Pooled proportion,§ 0.039 (0.001–0.171)		Low
Maternal bleeding											
2***	Cohort	No serious limitations	No important inconsistency	No problems	Some‡ imprecision	None	Not available	1/94 (1.1)	Pooled proportion,§ 0.017 (0.001–0.052)		Low
LMWH vs no prophylaxis											
Fetal loss											
1‖	Cohort	Some¶ limitations	No important inconsistency	No problems	No imprecision	None	No strong association	11/37 (29.7); 27/48 (56.3)	0.53 (0.30–0.92)	264 per 1,000	Low
Preeclampsia											
1‖	Cohort	Some¶ limitations	No important inconsistency	No problems	Large# imprecision (−2)	None	No strong association	2/26 (7.7); 1/26 (3.8)	2.00 (0.190–20.72)	Not** significant	Low
Aspirin vs LMWH											
Fetal loss											
1††	RCT	Some¶ limitations	No important inconsistency	No problems	No imprecision	None	Very strong ‡‡ association	57/80 (71.3); 11/80 (13.8)	5.18 (2.94–9.13)	575 per 1,000 (increased risk)	High
IUGR											
1††	RCT	Some¶ limitations	No important inconsistency	No problems	Some‡ imprecision	None	Strong§§ association	7/23 (30.4); 7/71 (9.9)	3.09 (1.21–7.87)	206 per 1,000 (increased risk)	Low
Preeclampsia											
1††	RCT	Some¶ limitations	No important inconsistency	No problems	Large# imprecision (−2)	None	No strong association	3/80 (3.8); 4/80 (5.0)	.75 (0.17–3.24)	Not** significant	Low
LMWH (enoxaparin 40 g/d) vs LMWH (enoxaparin 80 g/d)											
Fetal loss											
1‖‖	RCT	Some¶ limitations	No important inconsistency	No problem	Some¶¶ imprecision	None	No strong association	19/89 (21.3); 26/91 (28.6)	0.75 (0.45–1.25)	Not** significant	Low
IUGR											
1‖‖	RCT	Some¶ limitations	No important inconsistency	No problem	Large## imprecision (−2)	None	No strong association	7/65 (10.8); 5/63 (7.9)	1.36 (0.45–4.05)	Not** significant	Low
Preeclampsia											
1‖‖	RCT	Some¶ limitations	No important inconsistency	No problem	Large## imprecision (−2)	None	No strong association	3/89 (3.4); 4/91 (4.4)	0.77 (0.18–3.33)	Not** significant	Low

Table 12—*Continued*

Quality Assessment							Summary of Findings				
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Association	Treatment, No./Total (%)	Effect, RR (95% CI)	Events Prevented per 1,000 Treated	Quality
Placental abrubtion											
1‖‖	RCT	Some¶ limitations	No important inconsistency	No problem	Large## imprecision (−2)	None	No strong association	4/89 (4.5); 3/91 (3.3)	1.36 (0.31–5.92)	Not** significant	Low
Maternal bleeding											
1‖‖	RCT	Some¶ limitations	No important inconsistency	No problem	Large## imprecision (−2)	None	No strong association	0/89; 0/91	Not calculated	Not** significant	Low

*Includes Kupferminc et al[200]/2001, Tzafettas et al[206]/2005, and Brenner et al[198]/2000.
†One study finds zero proportion.
‡< 20 events.
§Calculated using inverse variance weighted proportional metaanalysis (DerSimonian-Laird).
‖Includes Carp et al[199]/2003.
¶Some methodological limitations; see Methods Table in online supplemental material.
#95% CI includes no effect and < 10 events.
**95% CI includes no effect. Events per 1,000 treated not calculated.
††Includes Gris et al[205]/2004.
‡‡RR = 5.18.
§§RR = 3.09, but no upgrading due to methodological limitations and < 20 events.
‖‖Includes Brenner et al[201]/2005 and Brenner et al[202]/2005.
¶¶95% CI includes no effect.
##95% CI includes no effect and < 20 events.
***Includes Kupferminc et al[200]/2001 and Brenner et al[198]/2000.

Table 13—*Frequency of Maternal Complications Reported With Various Anticoagulation Regimens in Pregnant Women With Prosthetic Valves**

Anticoagulation Regimen	TEC	Death (All Causes)	Comments
Vitamin K antagonists throughout, with/without heparin near term	31/788 (3.9)	10/561 (1.8)	8 cases of TEC occurred on heparin (6 on IV or adjusted dose, 2 on low dose)
Heparin use in first trimester, then vitamin K antagonists throughout with/without heparin near term	21/229 (9.2)	7/167 (4.2)	All 21 cases of TEC occurred on heparin (10 on IV or adjusted dose, 10 on low dose, dose unknown in 1 case)
Heparin throughout			
Adjusted-dose heparin	4/16 (25.0)	1/15 (6.7)	
Low-dose heparin	3/5 (60.0)	2/5 (40.0)	
Total	7/21 (33.3)	3/20 (15.0)	
No anticoagulation			
Nothing	6/38 (15.8)	2/37 (5.4)	
Antiplatelet agent	20/69 (29.0)	3/69 (4.4)	
Total	26/107 (24.3)	5/106 (4.7)	

*Data are presented as No./total (%). TEC = thromboembolic complications. Data are from Chan et al.[4]

UFH and LMWH for women at very high risk of preeclampsia. An effect of anticoagulant therapy on the risk of preeclampsia is biologically plausible via a reduction in thrombosis formation but also because LMWH has been shown to have an antiapoptotic effect on trophoblasts,[216] the source of the 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.[217] In a randomized trial of 80 nonthrombophilic women considered to be at increased risk of preeclampsia on the basis of both prior history and an underlying angiotensin-converting enzyme insertion/deletion polymorphism that examined the effect of prophylactic LMWH (dalteparin 5,000 U/d) on the pregnancy outcome, maternal BP, and on uteroplacental flow[218]; women receiving LMWH had a lower incidence of adverse outcomes with a 74.1% reduction in preeclampsia (RR, 0.26; 95% CI, 0.08 to 0.86) and a 77.5% reduction in IUGR (RR, 0.14; 95% CI, 0.03 to 0.56). Systolic and diastolic BPs, as well as the resistance indexes of both uterine arteries, were also significantly lower in the treated group. It is not clear if this effect of LMWH on prevention of preeclampsia is generalizable to women deemed to be at increased risk of preeclampsia because of history alone or the presence of other clinical risk factors.

Recommendations

10.1.1. For women considered high risk for preeclampsia, we recommend that low-dose aspirin throughout pregnancy (Grade 1B)**.**

10.1.2. For women with a history of preeclampsia, we suggest that UFH and LMWH should not be used as prophylaxis in subsequent pregnancies (Grade 2C)**.**

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

The management of pregnant women with mechanical prosthetic valves is a challenge. Antithrombotic therapy is essential because the risk of valve thrombosis and death or systemic embolism is high if it is not given (see the chapter "Valvular and Structural Heart Disease"). However, as outlined in Section 2.1 and Table 2, the use of vitamin K antagonists during pregnancy carries the potential for serious 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. Unfortunately, properly designed trials have not been performed and in the face of limited data, management remains controversial.

11.1 Anticoagulant Management of Mechanical Prosthetic Valves in Pregnant Women

Maternal outcomes derived from Chan and colleagues' systematic review of the literature examining outcomes in pregnant women with prosthetic valves[4] are presented in Table 13. The overall pooled of maternal mortality rate was 2.9%, while major bleeding occurred in 2.5% of all pregnancies, mostly at the time of delivery.[4] The regimen associated with

the lowest risk of valve thrombosis/systemic embolism (3.9%) was the use of vitamin K antagonists throughout pregnancy. Using UFH only between 6 weeks and 12 weeks of gestation was associated with an increased risk of valve thrombosis (9.2%).[4] The risk of thromboembolic complications was highest when heparin was used throughout pregnancy (33.3%) and events occurred in women receiving IV or adjusted dose subcutaneous heparin, as well as in those treated with low-dose heparin. Additional studies have been published subsequent to this analysis that also reported fewer thromboembolic events in women receiving warfarin than in those treated with heparin[11,219]; however, other authors report conflicting findings.[220] Although these data suggest that vitamin K antagonists are more efficacious 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 or use of an inappropriate target aPTT range.

LMWH has potential advantages over UFH in terms of maternal side effect profile, and there is increasing use of LMWH in pregnant women with prosthetic heart valves.[221–227] However, treatment failures have been reported.[223–227] The safety of LMWH for this indication has been questioned in a warning from a LMWH manufacturer.[228] This warning is based on postmarketing reports of valve thrombosis in an undisclosed number of patients receiving this LMWH, as well as by clinical outcomes in a open randomized study comparing LMWH (enoxaparin) with warfarin and UFH in pregnant women with prosthetic heart valves. The study was terminated after 12 of planned 110 patients were enrolled because of two deaths in the enoxaparin arm. Based on the small numbers in the trial and the inability to determine accurate incidence rates from postmarketing data, the true incidence of valve thrombosis in enoxaparin-treated pregnant women with mechanical valves and whether thrombosis rates are higher in such women than in warfarin-treated nonpregnant patients are unknown. Oran and colleagues performed a comprehensive search of the literature and reviewed the risks of maternal and fetal complications in pregnant women with mechanical heart valves treated with LMWH.[229] Valve thrombosis occurred in seven of 81 pregnancies (8.64%; 95% CI, 2.52–14.76%), and the overall thromboembolic rate was 12.35% (10 of 81 cases; 95% CI, 5.19–19.51%). However, 9 of the 10 patients with thromboembolic complications received a fixed dose of LMWH, and in 2 of these a fixed low dose was used. Among 51 pregnancies in which anti-factor Xa LMWH levels were monitored, only one patient was reported to have had a thromboembolic complication. The live birth rate was 87.65% (95% CI, 80.49–94.81%), and there were no reported congenital anomalies. Thus, LMWH may provide adequate protection provided that therapy is closely monitored and the dose-adjusted to maintain target anti-Xa levels.

There is no single accepted treatment option for physicians managing pregnant women with mechanical prosthetic valves. Given the limited and sometimes conflicting data, several approaches remain acceptable: (1) vitamin K antagonists throughout pregnancy (despite medicolegal concerns) with LMWH or UFH substitution close to term, (2) either LMWH or UFH between 6 weeks and 12 weeks and close to term only and vitamin K antagonists at other times, (3) aggressive dose-adjusted UFH throughout pregnancy, or (4) aggressive adjusted-dose LMWH throughout pregnancy. The decision as to 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, the option of vitamin K antagonist use throughout pregnancy might be a reasonable option in a very high-risk patient (*eg*, first-generation mechanical valve in the mitral position, history of thromboembolism, or associated atrial fibrillation). If warfarin is used, the dose should be adjusted to a target INR of 3.0 (range 2.5–3.5); a lower therapeutic range of 2.0–3.0 can be used in patients with bileaflet aortic valves, provided they do not have atrial fibrillation or left ventricular dysfunction. If subcutaneous UFH is used, it should be initiated in high doses (17,500–20,000 U q12h) and adjusted to prolong a 6-h postinjection aPTT into the therapeutic range. If LMWH is used, it should be administered twice daily and dosed to achieve the manufacturer's peak anti Xa level 4 h after subcutaneous injection (approximately 1.0 U/mL). Extrapolating from data in nonpregnant patients with mechanical valves receiving warfarin therapy,[230] for the same high risk women, the addition of aspirin, 75–100 mg/d, can be considered in an attempt to reduce the risk of thrombosis, recognizing that it increases the risk of bleeding.

Recommendations

11.1.1. For pregnant women with mechanical heart valves, we recommend that the decision about anticoagulant management during pregnancy include an assessment of additional risk factors for thromboembolism including valve type, position, and history of thromboembolism, and that the decision should also be influenced strongly by patient preferences (Grade 1C).

11.1.2. For pregnant women with mechanical

heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation:

(a) adjusted-dose bid LMWH throughout pregnancy (Grade 1C)**. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h after subcutaneous injection,** (Grade 2C) **or**

(b) adjusted-dose UFH throughout pregnancy administered subcutaneously q12h 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 U/mL, (Grade 1C) **or**

(c) UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed (Grade 1C)**.**

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, after a thorough discussion of the potential risks and benefits of this approach (Grade 2C)**.**

Underlying values and preferences: In contrast to our other recommendations, which place a high value on avoiding fetal risk, the recommendation for women at very high risk of thromboembolism places equal value on avoiding maternal complications.

Remark: For all the recommendations above, usual long-term anticoagulants should be resumed postpartum.

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

Conclusions

During pregnancy, anticoagulant therapy is indicated 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 APLAs. The use of anticoagulation for prevention of pregnancy complications in women with hereditary thrombophilia is becoming more frequent.

The use of anticoagulant therapy during pregnancy is challenging because the potential for fetal, as well as maternal, complications must be considered. LMWH, UFH and the heparinoid, danaparoid, are safe for the fetus. Vitamin K antagonists are fetopathic but the true risks of warfarin embyropathy and CNS abnormalities remain unknown. There is considerable evidence that coumarin embryopathy occurs only when vitamin K antagonists are administered between the sixth week and twelfth week of gestation. There is still debate about the safety of aspirin during the first trimester and only limited data are available about the safety of new anticoagulants (*eg*, direct thrombin inhibitors, fondaparinux) during pregnancy.

Although doubt has been raised about the effectiveness of UFH or LMWH for the prevention of systemic embolism in patients with mechanical heart valves, the observed failures with these anticoagulants could have been caused by inadequate dosing. Optimum management of pregnant women with thrombophilia (asymptomatic, as well as those with prior pregnancy complications and/or VTE) remains unknown.

The majority of studies used to support the recommendations in this publication are uncontrolled studies or case series. Many of the available controlled studies have important methodologic limitations. Although clinical trials involving pregnant women are very difficult to perform, there is a clear need for methodologically rigorous studies in this patient population.

Conflict of Interest Disclosures

Dr. Bates discloses grant monies received from the Canadian Institute of Health Research, the Heart and Stroke Foundation of Ontario, and bioMérieux. She received consultant fees from, and was on advisory committees for, GlaxoSmithKline, Dade Behring, and Trinity Biotech. Dr. Bates also has received an honorarium from LEO Pharma.

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Dr. Pabinger discloses that she has received grant monies from CSL Behring and Pfizer. She is also on the speaker bureaus for CSL Behring, Bayer, Pfizer, Aventis, Baxter, and Biotest, and is on advisory committees for Novo, Bayer, and Wyeth. Dr. Pabinger also holds a fiduciary position on the Board of Gesellschaft für Thrombose und Hämostaseforschung.

Dr. Hirsh discloses that he has received partial support for writing two books, one on fondaparinux and one on low-molecular-weight heparin.

Dr. Sofaer reveals no real or potential conflicts of interest or commitment.

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