Use of Antithrombotic Agents During Pregnancy

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about the use of antithrombotic agents during pregnancy is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004; 126: 179S–187S*). Among the key recommendations in this chapter are the following: for women requiring long-term vitamin K antagonist therapy who are attempting pregnancy, we suggest performing frequent pregnancy tests and substituting unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for warfarin when pregnancy is achieved (Grade 2C). In women with acute venous thromboembolism (VTE), we recommend adjusted-dose LMWH throughout pregnancy or IV UFH for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy and at least 6 weeks postpartum (Grade 1C+). In patients with a single episode of VTE associated with a transient risk factor that is no longer present, we recommend antepartum clinical surveillance and postpartum anticoagulants (Grade 1C). In patients with a single episode of VTE and thrombophilia or strong family history of thrombosis and not receiving long-term anticoagulants, we suggest antepartum prophylactic or intermediate-dose LMWH or minidose or moderate-dose UFH, plus postpartum anticoagulants (Grade 2C). In patients with multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants, we suggest antepartum adjusted-dose UFH or adjusted-dose LMWH followed by long-term anticoagulants postpartum (Grade 2C). For pregnant patients with antiphospholipid antibodies (APLAs) and a history of two or more early pregnancy losses or one or more late pregnancy losses, preeclampsia, intrauterine growth retardation, or abruption, we suggest antepartum aspirin plus minidose or moderate-dose UFH or prophylactic LMWH (Grade 2B). We suggest one of the following approaches for women with APLAs without prior VTE or pregnancy loss: surveillance, minidose heparin, prophylactic LMWH, and/or low-dose aspirin, 75 to 325 mg/d (all Grade 2C). In women with prosthetic heart valves, we recommend adjusted-dose bid LMWH throughout pregnancy (Grade 1C), aggressive adjusted-dose UFH throughout pregnancy (Grade 1C), or UFH or LMWH until the thirteenth week and then change to warfarin until the middle of the third trimester before restarting UFH or LMWH (Grade 1C). In high-risk women with prosthetic heart valves, we suggest the addition of low-dose aspirin, 75 to 162 mg/d (Grade 2C).

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Fatal pulmonary embolism (PE) remains a leading cause of maternal mortality in the Western world.[1] Maternal mortality from PE can be reduced in two ways: (1) by investigating women aggressively when they present with a clinical suspicion of deep vein thrombosis (DVT) or PE, and treating those with a diagnosis of venous thromboembolism (VTE); and (2) by prophylaxis of those who have an increased risk for DVT and/or PE. Both approaches are problematic for several reasons, the former because the symptoms and signs compatible with DVT and PE are common during pregnancy and are usually nonthrombotic in origin, reflecting physiologic changes rather than VTE. In support of this, the prevalence of DVT in a study[2] of consecutive pregnant patients presenting with a clinical suspicion was < 10%, compared to approximately 25% in studies[3–6] of nonpregnant populations. Further, in a study by Chan and colleagues,[7] only 2 of 113 pregnant subjects (1.8%) with suspected PE had high-probability ventilation perfusion lung scan results; 83 patients (73%) had normal perfusion scan results, and 28 patients (25%) had nondiagnostic scans, compared to approximately 10 to 30% of nonpregnant patients who present with suspected PE.[8,9] Potential alterations in the utility of tests used to diagnose DVT produced by the compressive effects of the gravid uterus on the iliac vein contribute to the diagnostic challenge. In addition, there is concern about performing procedures (such as isotope lung and spiral CT scanning) that expose the fetus to radiation. Prophylaxis of DVT and PE is problematic because it involves long-term parenteral unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Both are expensive, inconvenient, and painful to administer, and are associated with risks for bleeding,

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osteoporosis, and heparin-induced thrombocytopenia (HIT), although these complications, particularly HIT, are very uncommon with LMWH. Furthermore, rational administration of prophylaxis depends on identifying those women who have an increased risk of thrombosis and accurately quantifying this risk. Until recently, reliable information on the true incidence of recurrence in pregnant women with a single prior VTE event was not available. In addition, although many women with prior VTE have an identifiable laboratory abnormality associated with thrombophilia, the significance of these abnormalities and the management of such individuals remain controversial.

Since our last review, new information has been published on the management of pregnant women with prior VTE, the management of VTE in pregnancy, the safety of LMWH during pregnancy (particularly with regard to osteoporosis), the difficulties of managing pregnant women with prosthetic heart valves, and the relation between thrombophilia and fetal loss, intrauterine growth restriction (IUGR), and preeclampsia. In this chapter, we will review the management of thromboembolic complications 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.

Epidemiology of VTE During Pregnancy

The true incidence of VTE associated with pregnancy is unknown, but there is a strong clinical impression that the risk is increased compared to nonpregnant individuals.[10,11] There does not appear to be a preponderance of VTE in any trimester, although there is a striking predisposition for DVT to occur in the left leg (approximately 90%),[12] possibly because during pregnancy there is an exaggeration of the compressive effects on the left iliac vein by the right iliac artery where they cross.[13] The increased risk for VTE persists postpartum; available evidence suggests that the risk of VTE is higher after cesarean section (particularly emergency cesarean section) than after vaginal delivery.[11]

Anticoagulant Therapy During Pregnancy

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE, for the prevention and treatment of systemic embolism in patients with mechanical heart valves and, often in combination with aspirin, for the prevention of pregnancy complications in women with antiphospholipid antibodies (APLAs) or other thrombophilia and previous pregnancy complications. Given the paucity of data regarding the efficacy of anticoagulants during pregnancy, recommendations about their use during pregnancy are based largely on extrapolations from data from nonpregnant patients, from case reports, and from case series of pregnant patients. The antithrombotics currently available for the prevention and treatment of VTE and arterial thromboembolism include heparin and heparin-like compounds (UFH, LMWH, and heparinoids), coumarin derivatives, and aspirin. The "direct" thrombin inhibitors, such as hirudin, cross the placenta and have not yet been evaluated during pregnancy and, therefore, will not be further discussed.

Based on safety data, a heparin-related compound (LMWH or UFH) is the anticoagulant of choice during pregnancy for situations in which its efficacy is established. There is accumulating experience with the use of LMWHs and heparinoids, both in pregnant and nonpregnant patients, for the prevention and treatment of VTE.[14–28] Based on the results of large clinical trials in nonpregnant patients, LMWH and heparinoids (danaparoid sodium) are at least as effective and safe as UFH for the treatment of patients with acute proximal DVT,[23–25] and for the prevention of DVT in patients who undergo surgery.[26] There is evidence that LMWH (and heparinoids) do not cross the placenta,[29,30] and an overview and large series of cases concluded that LMWH was safe for the fetus.[22,31]

LMWHs have potential advantages over UFH during pregnancy because they cause less HIT,[32] have a longer plasma half-life and a more predictable dose response than UFH,[27] with the potential for once-daily administration, and are likely associated with a lower risk of heparin-induced osteoporosis.[33,34] Allergic skin reactions to both LMWH and UFH can occur.[21,35] These take the form of itchy, erythematous infiltrated plaques, which may resolve when preparations are switched, although cross-reactivity can occur. As HIT can present with isolated skin manifestations, this entity should be excluded when skin lesions develop.

Fetal Complications of Anticoagulants During Pregnancy

There are two potential fetal complications of maternal anticoagulant therapy: teratogenicity and bleeding. Neither UFH[36] nor LMWH[29,30] cross the placenta; therefore, these agents do not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible. Several studies[22,31,37,38] strongly suggest that UFH/LMWH therapy is safe for the fetus.

In contrast, coumarin derivatives cross the placenta and have the potential to cause both bleeding in the fetus and teratogenicity.[37,39] Coumarin derivatives can cause an embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses, after *in utero* exposure to vitamin K antagonists (VKAs) during the first trimester of pregnancy, and CNS abnormalities after exposure to such drugs during any trimester.[39] It is probable that these agents are safe during the first 6 weeks of gestation, but there is a risk of embryopathy if coumarin derivatives are taken between 6 weeks and 12 weeks of gestation.[39] Although one cohort study[40] reported that the use of coumarins during the second and third trimester was not associated with major risks for abnormalities in growth and long-term development of offspring, the authors did note that neurodevelopmental problems were found more often in children exposed to coumarins in the second and third trimester of pregnancy. In addition, VKAs cause an anticoagulant

Table 1—Question Definition and Eligibility Criteria for the Use of Antithrombotic Agents During Pregnancy*

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
1.0	Fetuses, children of women using a coumarin derivative during pregnancy	Coumarin exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Fetuses, children of women using UFH or LMWH during pregnancy	UFH or LMWH exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations, heparin levels in umbilical cord blood	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Fetuses, children of women using aspirin during pregnancy	Aspirin exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations, patent ductus arteriosus	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Fetuses, children of women using danaparoid during pregnancy	Danaparoid exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations, heparin levels in umbilical cord blood	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Fetuses, children of women using direct thrombin inhibitors during pregnancy	Direct thrombin inhibitor exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations, aPTT, prothrombin time, or INR of umbilical cord blood	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Fetuses, children of women using direct thrombin inhibitors during pregnancy	Pentasaccharide exposure *in utero*	Fetal hemorrhage, fetal loss, congenital malformations, heparin levels in umbilical cord blood	Observational studies	Comorbid condition associated with adverse fetal outcome
1.0	Breast-feeding infants of women receiving coumarin therapy	Coumarin exposure during breastfeeding	Infant hemorrhage, coumarin levels/prothrombin time results on breast milk, infant blood	Observational studies	Comorbid condition associated with adverse neonatal outcome
1.0	Breast-feeding infants of women receiving UFH or LMWH	UFH or LMWH exposure during breastfeeding	Infant hemorrhage, heparin levels, aPTT results in breast milk, infant blood	Observational studies	Comorbid condition associated with adverse neonatal outcome
1.0	Pregnant women receiving UFH	UFH therapy during pregnancy	Maternal hemorrhage, maternal HIT, maternal heparin-associated osteoporosis, maternal death	RCT, observational study, systematic review	
1.0	Pregnant women receiving LMWH	LMWH therapy during pregnancy	Maternal hemorrhage, maternal HIT, maternal heparin-associated osteoporosis, maternal death	RCT, observational study, systematic review	
2.0	Pregnant women with VTE	UFH or LMWH	Recurrent VTE during same pregnancy or in 6 wk postpartum	RCT, observational studies	
3.1	Pregnant women with a prior history of VTE	Natural history (no intervention, time is exposure)	Recurrent VTE during pregnancy or in 6 wk postpartum	Observational studies	Comorbid condition associated with VTE
3.1 (if answer to above yes, probably, or possibly)	Pregnant women with a prior history of VTE	UFH or LMWH with or without aspirin	Recurrent VTE during pregnancy or in 6 wk postpartum	RCT, observational studies	
3.2	Women with thrombophilia (APLAs, factor V Leiden, prothrombin gene mutation, hyperhomocysteinemia, protein S deficiency, protein C deficiency, antithrombin deficiency)	Natural history (no intervention, time is exposure)	VTE during pregnancy or 6 wk postpartum	Observational studies	Comorbid condition associated with VTE

Table 1—*Continued*

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
3.2 (if answer to above yes, probably, possibly)	Pregnant women with thrombophilias as above	UFH, LMWH, warfarin	VTE during pregnancy or 6 wk postpartum	RCT, observational studies	Comorbid condition associated with VTE
4.0	Pregnant women with thrombophilia (APLAs, factor V Leiden, prothrombin gene mutation, hyperhomocysteinemia, protein S deficiency, protein C deficiency, antithrombin deficiency)	Natural history (no intervention, time is exposure)	First trimester fetal loss, second trimester fetal loss, third trimester fetal loss, IUGR, preeclampsia, placental abruption	Observational studies	Comorbid condition associated with pregnancy loss
4.0 (if above yes, probably, possibly)	Pregnant women with thrombophilias as above	UFH or LMWH with or without aspirin	First trimester fetal loss, second trimester fetal loss, third trimester fetal loss, IUGR, preeclampsia, placental abruption	RCT, observational studies	Comorbid condition associated with pregnancy loss
5.0	Pregnant women with mechanical valves	Coumarin derivatives throughout pregnancy	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities (including warfarin embryopathy), fetal loss	RCT, observational study	
5.0	Pregnant women with mechanical valves	UFH throughout pregnancy	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities, fetal loss	RCT, observational study	
5.0	Pregnant women with mechanical valves	LMWH throughout pregnancy	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities, fetal loss	RCT, observational study	
5.0	Pregnant women with mechanical valves	Coumarin derivatives substituted with UFH or LMWH during the first trimester (at or before 6 wk gestation)	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities (including warfarin embryopathy), fetal loss	RCT, observational study	
5.0	Pregnant women with mechanical valves	Coumarin derivatives substituted with UFH or LMWH during the first trimester (after 6 wk gestation)	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities (including warfarin embryopathy), fetal loss	RCT, observational study	
5.0	Pregnant women with mechanical valves	Aspirin only (compared to anticoagulation) throughout pregnancy	Maternal thromboembolism, maternal bleeding, maternal death, congenital abnormalities, fetal loss	RCT, observational study	

*RCT = randomized controlled trial.

effect in the fetus, which is a concern, particularly at the time of delivery, when the combination of the anticoagulant effect and trauma of delivery can lead to bleeding in the neonate.

Maternal Complications of Anticoagulant Therapy During Pregnancy

In a cohort study,[38] the rate of major bleeding in pregnant patients treated with UFH therapy was 2%, which is consistent with the reported rates of bleeding associated with heparin therapy in nonpregnant patients[41] and with warfarin therapy[42] when used for the treatment of DVT. During pregnancy, the activated partial thromboplastin time (aPTT) response to heparin is often attenuated because of increased levels of factor VIII and fibrinogen.[43] Adjusted-dose subcutaneous (SC) UFH can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use prior to labor.[44] In a small study,[44] an anticoagulant effect persisted for up to 28 h after the last injection of adjusted-dose SC UFH, resulting in deliveries that were complicated by a prolonged aPTT. The mechanism for this prolonged effect is unclear. Bleeding complications appear to be very uncommon with LMWH.[14–22,28,34,45]

HIT

Approximately 3% of nonpregnant patients receiving UFH acquire immune, IgG-mediated thrombocytopenia, which is frequently complicated by extension of preexisting VTE or new arterial thrombosis.[32] This should be differentiated from an early, benign, transient thrombocytopenia that can occur with initiation of UFH. Diagnosing immune thrombocytopenia is often difficult because definitive platelet-activation assays are not widely available and turnaround times are slow. It 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.[32] In pregnant women who acquire HIT and require ongoing anticoagulant therapy, use of the heparinoid danaparoid sodium is recommended because it is an effective antithrombotic agent,[25] does not cross the placenta, and has much less cross-reactivity with UFH and, therefore, less potential to produce recurrent HIT than LMWH.[46]

Heparin-Induced Osteoporosis

Long-term heparin therapy has been reported to cause osteoporosis in both laboratory animals and humans.[47–51] A number of studies have attempted to quantify the risk of osteoporosis when heparin is administered for periods of ≥ 1 month. In general, symptomatic vertebral fractures have been reported to occur in approximately 2 to 3% of the patient population, and significant reductions in bone density have been reported in up to 30% of patients receiving long-term UFH.[47] Dahlman[48] studied 184 women receiving long-term prophylactic UFH therapy during pregnancy, and reported a 2.2% incidence of vertebral fracture. In contrast, in a small randomized trial,

Monreal et al[33] reported spinal fractures in 6 of 40 nonpregnant patients (15%) receiving 10,000 IU UFH SC bid for a period of 3 to 6 months. The higher incidence of osteoporotic fractures in the latter study[33] is probably due to the fact that these patients were significantly older than those in the study by Dahlman et al.[48]

In animal studies, UFH has been shown to cause a dose-dependent loss of cancellous bone through decreasing rates of bone formation and increased bone resorption.[49] Animal models demonstrating that heparin is sequestered in the bone for extended periods also suggest that heparin-induced osteoporosis may not be rapidly reversible.[50]

Several lines of evidence now suggest that LMWHs have a lower risk of osteoporosis than heparin. In the study by Monreal et al,[33] dalteparin, 5,000 IU anti-Xa SC bid, was compared with UFH, 10,000 IU SC bid, in 80 patients with DVT. Both treatments were administered for a period of 3 to 6 months. Six of the 40 patients (15%; 95% confidence interval [CI], 6 to 30%) who received UFH acquired spinal fractures compared with only 1 of 40 patients (3%; 95% CI, 0 to 11%) receiving dalteparin. Further, in a randomized trial[34] comparing UFH and dalteparin for thromboprophylaxis in pregnancy that measured bone mineral density in the lumbar spine for up to 3 years after delivery, bone density did not differ between healthy control subjects and the dalteparin group. Density was significantly lower in the UFH group when compared to both control subjects and dalteparin-treated women. Multiple logistic regression found that the type of heparin therapy was the only independent factor associated with reduced bone mass.[34] Cohort studies[31] have also reported no association with osteoporosis and LMWH therapy. A study[51] using an animal model of heparin-induced osteoporosis support the hypothesis that LMWHs cause less osteoporosis than UFH. When rats were treated with once-daily SC injections of either UFH (1.0 U/g or 0.5 U/g) or LMWH (tinzaparin 1.0 U/g or 0.5 U/g) for a period of 32 days, both treatments decreased cancellous bone volume in a dose-dependent fashion, but UFH caused significantly more cancellous bone loss than LMWH.

Use of Anticoagulants in the Nursing Mother

Heparin and LMWHs are not secreted into breast milk and can be safely administered to nursing mothers.[52] There have been two convincing reports[53,54] that warfarin does not induce an anticoagulant effect in the breast-fed infant when the drug is given to a nursing mother. Therefore, the use of warfarin in women who require postpartum anticoagulant therapy is also safe, and women using this drug should be encouraged to breast feed.

Safety of Aspirin During Pregnancy

Potential complications of aspirin during pregnancy include birth defects and bleeding in the neonate and in the mother. Both a metaanalysis[55] and a large randomized trial[56] that enrolled $> 9,000$ patients reported that low-dose (60 to 150 mg/d) aspirin therapy administered during the second and third trimesters of pregnancy in women at

risk for pregnancy-induced hypertension or IUGR was safe for the mother and fetus. Thus, based on current evidence, low-dose aspirin (< 150 mg/d) during the second and third trimesters appears to be safe. The safety of higher doses of aspirin and/or aspirin ingestion during the first trimester remains uncertain.

1.0 Management Of Women Receiving Long-term VKA Therapy Who Are Considering Pregnancy

As described above VKAs have the potential to cause teratogenicity.[37,39] It appears that the risk of fetal complications is reduced if coumarin derivatives are stopped before the sixth week of gestation.[39] Women receiving VKA therapy should be counseled about the risks of warfarin therapy and pregnancy before pregnancy occurs. If pregnancy is still desired, two options can be considered: (1) performance of frequent pregnancy tests and substitution of adjusted-dose UFH or LMWH for warfarin when pregnancy is achieved, or (2) replacement of warfarin with UFH or LMWH before conception is attempted. Both approaches have limitations; the first assumes that warfarin is safe during the first 4 to 6 weeks of gestation and requires a reliable patient. The second increases the duration of exposure to heparin and, therefore, is costly and exposes the patient to a higher risk of osteoporosis (at least with UFH). We suggest the first approach because it is convenient and appears to be safe.

Recommendation

1.1. For women requiring long-term VKA therapy who are attempting pregnancy, we suggest performing frequent pregnancy tests and substituting UFH or LMWH for warfarin when pregnancy is achieved (**Grade 2C**).

2.0 Treatment of VTE During Pregnancy

There are now many well-designed randomized trials and meta-analyses[23,24] comparing IV UFH and SC LMWH for the treatment of acute DVT and PE in nonpregnant patients. They show that LMWH is at least as safe and effective as UFH. There are also studies[57–59] in nonpregnant patients showing that long-term LMWH (and UFH) are as effective and safe as warfarin for the prevention of recurrent VTE. Therefore, in the pregnant patient with acute VTE, two alternative approaches are reasonable: (1) IV UFH followed by at least 3 months of SC LMWH or adjusted-dose SC UFH, or (2) adjusted-dose SC UFH or LMWH can be used both for initial and long-term treatment. With UFH, doses should be adjusted to prolong a mid-interval aPTT into the therapeutic range (adjusted-dose SC heparin).

As discussed above, better bioavailabilty, a better safety profile with regard to osteoporosis and thrombocytopenia compared to UFH, and the inconvenience associated with the need for frequent aPTT monitoring of UFH make LMWH the preferred option for most patients. Thus, in view of the totality of the data, we endorse the use of LMWH for initial and long-term treatment of acute VTE

in pregnant women. If one of these agents is used for acute treatment of VTE, a weight-adjusted dose regimen (as per the recommendations of the manufacturer) should be used. However, as the half-life of LMWH is decreased in pregnancy, twice-daily regimens are probably preferable to once-daily dosing. As the pregnancy progresses (and most women gain weight), the potential volume of distribution for LMWH changes. Two options are available to deal with this. The first is to simply change the dose in proportion to the weight change.[60] The second is to perform regular anti-factor Xa levels 3 to 4 h after the morning dose, and adjust the dose of LMWH to achieve an anti-Xa level of approximately 0.5 to 1.2 U/mL.[61,62] However, clinical experience suggests that few dose adjustments are required, and monitoring may not be necessary or need only be done infrequently.

It remains unclear whether the dose of LMWH or UFH can be reduced after an initial period of full anticoagulation. It has been suggested that therapeutic levels of 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 therapy is reduced after initial full-dose anticoagulation may reduce the risks of anticoagulant-related bleeding and heparin-induced osteoporosis, and have been successfully used in patients with contraindications to warfarin[33] and in patients with underlying malignancy.[63] Although there have been no studies directly comparing these two types of dosing strategies in pregnant women, this type of modified dosing regimen may be useful in pregnant women at increased risk of bleeding or osteoporosis.

In order to avoid an unwanted anticoagulant effect during delivery (especially with neuroaxial anesthesia) in women receiving adjusted-dose SC UFH therapy,[44] it is suggested that heparin be discontinued 24 h prior to elective induction of labor or cesarean section. If spontaneous labor occurs in women receiving adjusted-dose SC UFH, careful monitoring of the aPTT is required. If it is markedly prolonged near delivery, protamine sulfate may be required to reduce the risk of bleeding. Although bleeding complications appear to be very uncommon with LMWH,[14–22,28,34,45] we suggest the same approach to women receiving "therapeutic doses" of LMWH as in those receiving adjusted-dose UFH, namely discontinuing LMWH 24 h prior to elective induction of labor or cesarean section.

If the woman is deemed to have a very high risk of recurrent VTE (eg, proximal DVT within 2 weeks), therapeutic IV UFH can be initiated and discontinued 4 to 6 h prior to the expected time of delivery in order to limit the duration of time without therapeutic anticoagulation. In addition or alternatively, a temporary inferior vena cava filter can be inserted within a week of elective induction or cesarean section and removed postpartum. Postpartum anticoagulants should be administered for at least 6 weeks.

Recommendations

2.1. In women with acute VTE, we recommend either adjusted-dose LMWH throughout pregnancy or IV UFH

(bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Anticoagulants should be administered for at least 6 weeks postpartum (**Grade 1C+**).

2.2. In women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuing the heparin 24 h prior to elective induction of labor (**Grade 1C**).

3.0 Prevention of VTE During Pregnancy

When evaluating women who are deemed to have an increased risk of VTE, it is important to first critically examine the evidence that the women indeed had VTE and/or have thrombophilia placing them at increased risk of VTE. Once this is done, based on laboratory and clinical data, the women can be broadly categorized as follows: (1) single episode of VTE associated with a transient risk factor; (2) single idiopathic episode of VTE and not receiving long-term anticoagulants; (3) single episode of VTE and thrombophilia (confirmed laboratory abnormality) and not receiving long-term anticoagulants; (4) multiple (two or more) episodes of VTE and/or receiving long-term anticoagulants (*eg*, single episode of VTE—either idiopathic or associated with thrombophilia); and (5) no prior VTE and thrombophilia (confirmed laboratory abnormality). Risk assessment for each patient should be individualized. For example, a woman with a single episode of VTE in association with a transient risk factor might be managed more aggressively if she requires bed rest or is morbidly obese or has a family history of VTE.

3.1 Prior VTE and pregnancy

Women with a history of VTE (with or without thrombophilia) are believed to have a higher risk of recurrence in subsequent pregnancies. Estimates of the rate of recurrent venous thrombosis during pregnancy in women with a history of VTE have varied between zero and 13%.[64–67] The higher of these estimates has prompted authorities (including the American College of Chest Physicians) to recommend anticoagulant prophylaxis during pregnancy and the postpartum period in women with a history of VTE. However, the risk is likely to be lower than has been suggested by some of these studies because objective testing was used uncommonly to confirm the diagnosis of recurrent VTE, thereby resulting in a substantial overdiagnosis of recurrence. Furthermore, the higher estimates of the frequency of recurrence are from retrospective studies[66,67] of nonconsecutive patients, whereas the lower estimates come from prospective, albeit small (n = 20, n = 59), studies.[64,65]

In order to obtain a reliable estimate of the true incidence of recurrence in women with prior VTE, Brill-Edwards and Ginsberg[68] performed a prospective study of 125 pregnant women with a single previous episode of objectively diagnosed VTE. Antepartum heparin was withheld, and anticoagulants (usually warfarin with a target international normalized ratio [INR] of 2.0 to 3.0 with an initial short course of UFH or LMWH) were administered in the postpartum period for 4 to 6 weeks. The antepartum recurrence rate was 2.4% (95% CI, 0.2 to 6.9%). Ninety-five patients underwent blood testing to identify thrombophilia. There were no recurrences in the 44 patients (0%; 95% CI, 0.0 to 8.0%) who did not have thrombophilia and had a previous episode of thrombosis that was associated with a temporary risk factor. Patients with abnormal test results and/or a previous episode of thrombosis that was idiopathic (unprovoked) had an antepartum recurrence rate of 5.9% (95% CI, 1.2 to 16%). Based on these results, antepartum heparin prophylaxis is not routinely recommended 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 risk factors for VTE into account. Further studies are needed to determine whether prophylaxis is warranted in patients with laboratory thrombophilia and/or a previous episode of idiopathic thrombosis.

Based on the currently available studies, there are two general approaches to the antepartum management of pregnant patients with previous VTE who require active prophylaxis with UFH or LMWH. One randomized trial and several recent cohort studies[14–22,69] reported low recurrence rates with the use of prophylactic once-daily LMWH. Given the benefits of LMWH, it is the preferred choice. For prophylaxis of VTE during pregnancy, several dose regimens of LMWHs have been used. Common regimens that have been reported in a randomized trial[34] (comparing the effects of LMWH and UFH on bone density), cohort studies and case series include subcutaneous enoxaparin; dalteparin, 5,000 U q24h[69]; and dose-adjusted LMWH to achieve a peak anti-Xa level of 0.2 to 0.6 U/mL.[19–22] Although all of the studies reported low recurrence rates, none were placebo-controlled trials; therefore, the recurrence rates might have been low without prophylaxis.

SC UFH, 5,000 U q12h, is effective and safe for the prevention of VTE in high-risk nonpregnant patients,[70] and its use has been recommended in pregnant patients. However, there is concern that a dose of 5,000 U SC q12h may be insufficient in high-risk situations because it does not reliably produce detectable heparin levels. There are also published data that more intense 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.[48] Thus, where UFH is employed for prophylaxis in pregnancy, higher doses are often used, such as 10,000 IU 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, even with a sensitivity of 96% and a specificity of 98%, the positive predictive value of compression ultrasonography would be only 10%, if we postulate that the prevalence of recurrent VTE during pregnancy is approximately 5%. Second, the timing of screening with ultrasound is problematic. Even if performed as often as

weekly, a woman could still acquire 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 they be investigated aggressively if symptoms suspicious of DVT or PE occur.

Recommendations

3.1.1. In patients with a single episode of VTE associated with a transient risk factor that is no longer present, we recommend clinical surveillance and postpartum anticoagulants (**Grade 1C**). If the previous event is pregnancy or estrogen-related or there are additional risk factors (such as obesity), we suggest antenatal anticoagulant prophylaxis (**Grade 2C**).

3.1.2. In patients with a single idiopathic episode of VTE who are not receiving long-term anticoagulants, we suggest prophylactic LMWH, or minidose UFH or moderate-dose UFH, or clinical surveillance plus postpartum anticoagulants (**Grade 2C**).

3.1.3. In patients with a single episode of VTE and thrombophilia (confirmed laboratory abnormality) or strong family history of thrombosis and not receiving long-term anticoagulants, we suggest prophylactic or intermediate-dose LMWH or mini-dose or moderate-dose UFH, plus postpartum anticoagulants (**Grade 2C**).

3.1.4. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden and homozygotes for these conditions with a history of VTE, we suggest intermediate-dose LMWH prophylaxis or moderate-dose UFH (**Grade 2C**).

3.1.5. In patients with multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants (*eg*, single episode of VTE—either idiopathic or associated with thrombophilia) we suggest adjusted-dose UFH or adjusted-dose LMWH followed by resumption of long-term anticoagulants postpartum (**Grade 2C**).

3.1.6. In all women with previous DVT, antenatally and postpartum, we suggest use of graduated elastic compression stockings (**Grade 2C**).

See summary of recommendations for definitions of dosing regimens.

3.2 Thrombophilia and VTE associated with pregnancy

Approximately 50% of gestational VTEs are associated with heritable thrombophilia.[11] Studies[71–82] have provided estimates for the risk of gestational VTE in women with thrombophilia. The relative risks or odds ratios (ORs) for gestational thrombosis in women with antithrombin deficiency, heterozygosity for the factor V Leiden or prothrombin gene mutations, and homozygosity for the C667T methylene tetrahydrofolate reductase (MTHFR) mutation (thermolabile variant), after adjusting for other key variables, are presented in Tables 2, 3. Variability in these risk estimates is likely the result of small sample sizes; as well as differences in study methodology (case control[71,73,74,82] vs cohort[72,75]), the characteristics of control subjects (parous age-matched women without a history of thrombosis[82] vs age-matched women without a history of thrombosis with or without previous pregnancy[71] vs healthy women with at least one previous pregnancy without thrombosis[74] vs the general population[73]), and the factors adjusted for in calculating risk estimates (parity[74] vs age, body mass index, oral contraceptive use, protein C and S activity, and antithrombin activity, and presence of factor V Leiden, prothrombin G20210A, or MTHFR 677TT genotype[71]). Although not systematically examined in any of these studies, persistent APLAs[76] are probably also associated with an increased risk of VTE during pregnancy and the puerperium.

In a study of 119 women with gestational VTE and 233 control subjects, Gerhardt et al[71] also provided 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.[11] These values were 1:500 for individuals heterozygous for the factor V Leiden mutation, 1:200 for those heterozygous for the prothrombin 20210A allele, and 4.6:100 for double heterozygotes. In a similar analysis, a retrospective study[72] of 72,000 pregnancies, in which women with venous thrombosis were assessed for thrombophilia and where the underlying prevalence of these defects in the population was known, showed that 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.

Given that the background rate of VTE during preg-

Table 2—*Risk of VTE in Pregnancy in Patients With Thrombophilia**

Source	Design	Type of Antithrombin Deficiency	Antithrombin or Protein C or Protein S Deficiency	Factor V Leiden Heterozygous	Prothrombin G20210A Heterozygous	C677T MTHFR Homozygous	Any
McColl et al[73]	Retrospective case control	Quantitative, 282 (31–2,532); qualitative, 28 (5.5–142)	Not available	4.5 (2.1–14.5)	4.4 (1.2–16.0)	0.45 (0.13–1.6)	Not available

*Data are presented as OR (95% CI).

Table 3—Risk of VTE in Pregnancy or Puerperium in Patients With Thrombophilia*

Source	Design	Type of Antithrombin Deficiency	Antithrombin or Protein C or Protein S Deficiency	Factor V Leiden Heterozygous	Prothrombin G20210A Heterozygous	C677T MTHFR Homozygous	Any
Martinelli et al[74]	Case control	Not available	13.1 (5.0–34.5)	8.7 (3.4–22.5)	1.8 (0.6–5.4)	Not available	13.1 (5.0–34.5)
Gerhardt et al[71]	Case control	< 80% activity 10.4 (2.2–62.5)	Not available	6.9 (3.3–15.2)	9.5 (2.1–66.7)	1.0 (0.5–2.2)	Not available
Grandone et al[82]	Case control	Not available	Not available	16.3 (4.8–54.9)	10.2 (4.0–25.9)	2.1 (1.0–4.5)	Not available
Friederich et al[75]	Retrospective cohort	Not available	8.0 (1.2–184)	Not available	Not available	Not available	Not available

*Data are presented as OR or relative risk (95% CI).

nancy is approximately 1:1000,[11] the absolute risk of VTE remains modest for the majority of these thrombophilias, except antithrombin deficiency, homozygosity for the factor V Leiden mutation, and combined defects. The absolute risk of pregnancy-associated VTE has been reported to range from 9 to 16% in homozygotes for the factor V Leiden mutation.[77–80] Double heterozygosity for the factor V Leiden and prothrombin gene mutations has been reported to have an absolute risk of pregnancy-associated VTE of 4.0% (95% CI, 1.4 to 16.9%).[79] 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 inherited thrombophilias, especially in symptomatic kindreds.

Hyperhomocysteinemia is associated with an increased risk of VTE in nonpregnant subjects.[81] The data regarding homozygosity for MTHFR C677T in this situation is less definitive. It is also unclear whether homozygotes for MTHFR C677T have an increased risk of VTE during pregnancy and the puerperium.[71,73,82] 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.[83]

The antepartum 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. We are unaware of prospective data addressing the issue of the incidence of VTE in a large group of pregnant women with thrombophilia and no prior VTE.

Recommendations

3.2.1. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden, and homozygotes for these conditions with no prior VTE, we suggest active prophylaxis (**Grade 2C**).

3.2.2. In all other patients with no prior VTE and

thrombophilia (confirmed laboratory abnormality), we suggest surveillance or prophylactic LMWH or minidose UFH, plus postpartum anticoagulants (**Grade 2C**).

See summary of recommendations for definitions of dosing regimens.

3.3 VTE associated with cesarean section

Available data suggests that the risk of VTE is higher after cesarean section (especially emergent surgery) than after vaginal delivery.[11] The presence of additional risk factors for pregnancy-associated VTE (for example, prior VTE, thrombophilia, age > 35 years, obesity, prolonged bed rest, and concomitant acute medical illness) may exacerbate this risk. It has been recommended that graduated compression stockings be used during and after cesarean section in patients considered to be at "moderate risk" of VTE and that LMWH or UFH prophylaxis be added in those thought to be at "high risk."[84] However, there is insufficient good quality data to provide information as to the benefits associated with these interventions.[85,86]

4.0 Thrombophilia and Pregnancy Complications

It has been suggested that maternal thrombophilias are associated with pregnancy complications, including fetal loss, IUGR, preeclampsia, abruption, and intrauterine death.[87] There have now been many case-control and cohort studies[88–98] examining the relationship between some heritable thrombophilias and miscarriage. The results of the studies are inconsistent, reflecting different populations, small sample size, varying case definition, potential selection bias, and retrospective design. These issues have, at least in part, been resolved by a recent meta-analysis[99] of 31 cohort, case-control, and cross-sectional studies, in which the quality of the data was regarded as strong or moderate. This analysis reported an association between fetal loss and the presence of factor V Leiden, activated protein C resistance, protein S deficiency, and prothrombin G20210A.[99] For heterozygosity for the factor V Leiden mutation, pooled ORs were 1.73 (95% CI, 1.18 to 2.54) for nonrecurrent fetal loss, 2.01 (95% CI, 1.13 to 3.58) for recurrent loss before 13 weeks,

and 3.26 (95% CI, 1.82 to 5.83) for nonrecurrent late loss (after 19 weeks). For heterozygosity for the prothrombin G20210A allele, ORs were 2.15 (95% CI, 1.18 to 3.54) for recurrent fetal loss, 2.32 (95% CI, 1.12 to 4.79) for recurrent loss before 13 weeks, and 2.30 (95% CI, 1.09 to 4.87) for nonrecurrent late loss. Protein S deficiency was associated with an OR of 7.39 (95% CI, 1.28 to 42.83) for nonrecurrent late fetal loss. However, protein C and antithrombin deficiency, as well as homozygosity for MTHFR C677T, were not associated with recurrent or nonrecurrent fetal loss.

One systematic review and meta-analysis[100] reported a significant association between preeclampsia and the factor V Leiden mutation (heterozygotes and homozygotes), heterozygosity for the prothrombin G20210A allele, homozygosity for MTHFR C677T, and protein C and S deficiency. However, a more recent meta-analysis published in conjunction with a large population-based study did not find an association between preeclampsia and the presence of factor V Leiden, prothrombin G20210A, homozygosity for MTHFR C677T or platelet collagen receptor $\alpha 2\beta 1C807T$.[101] Although there was no overall association between preeclampsia and these thrombophilic states, there was an association between severe preeclampsia and heterozygosity for the factor V Leiden mutation and homozygosity for MTHFR C677T, with pooled ORs of 2.84 (95% CI, 1.95 to 4.14) and 1.50 (95% CI, 1.02 to 2.23), respectively. The reasons underlying these differences in results with regard to the association between thrombophilia and preeclampsia are unclear. It may reflect different diagnostic criteria, small sample size, and reporting bias, as many studies had relatively low levels of heterozygosity for factor V Leiden in the control groups studied. Nonetheless, these data suggest that while prothrombotic genotypes might not be causative factors for preeclampsia, they could be linked to the severity of disease expression once the condition arises.

A previous systematic review and meta-analysis[100] reported significant associations between IUGR and heterozygosity for the prothrombin G20210A allele, homozygosity for MTHFR C6777, and protein S deficiency. However a large, methodologically rigorous case-control study[102] has cast doubt on the association between IUGR and thrombophilia. This study of 493 newborns with IUGR and 472 controls found no increase in the risk of IUGR among mothers homozygous for MTHFR C677T, or those heterozygous for factor V Leiden or prothrombin G20210A with ORs of 1.55 (95% CI, 0.83 to 2.90), 1.18 (95% CI, 0.54 to 2.35), and 0.92 (95% CI, 0.36 to 2.35), respectively. Even when the birth weight centile was reduced to the fifth centile and the analysis repeated, there was no relationship with underlying thrombophilia, suggesting that, in contrast to preeclampsia, there is no association between thrombophilia and disease severity. However, there was an association between MTHFR C677T homozygosity and IUGR in the subgroup of mothers not receiving vitamin supplements (OR, 12.3; 95% CI, 1.2 to 126.2). Thus, the lack of association between IUGR and MTHFR C677T homozygosity may reflect the widespread use of multivitamin preparations containing folic acid in pregnancy, which could influence homocysteine

levels. This emphasizes the need for consideration of plasma homocysteine, rather than the MTHFR genotype alone, as a possible risk factor for pregnancy complications. In addition, this study[102] reported no association between the fetal genotype for thrombophilia and IUGR. The difference between this study and previous reports lie in its large sample size, which contained more patients than the total analyzed in the metaanalysis described above.

In view of these data, women with recurrent pregnancy loss, a second trimester miscarriage, or a history of intrauterine death or severe or recurrent preeclampsia should be screened for underlying congenital thrombophilias. However, in contrast to patients with APLA syndrome with recurrent miscarriage, where a combination of heparin and low-dose aspirin has been shown to be effective in reducing miscarriage rates, there are no convincing data to indicate whether such antithrombotic therapy is beneficial in women with congenital thrombophilia and pregnancy complications. Nevertheless, since many of these women also have an increased risk of VTE, antithrombotic therapy should be considered in this population. Randomized trials are assessing the value of this therapy in women with recurrent pregnancy loss and underlying thrombophilia. Although hyperhomocysteinemia has not been associated with DVT in pregnancy,[73] hyperhomocysteinemia[98] and reduced serum folic acid concentrations appear to be risk factors for recurrent spontaneous miscarriage; therefore, folic acid supplementation may be beneficial in such patients.

APLAs can be detected using clotting assays (lupus anticoagulant/nonspecific inhibitor) or immunoassays (anticardiolipin antibodies), and have been reported to occur in systemic lupus erythematosus, with use of certain drugs and in apparently healthy individuals.[103] There is convincing evidence that the presence of APLAs is associated with an increased risk of thrombosis[76] and pregnancy loss.[104,105] Thus, pregnant women with APLAs should be considered at risk for both of these complications. In addition, women with recurrent pregnancy loss should be screened for the presence of APLAs prior to, or during the early part of, pregnancy. The management of pregnant women with APLAs is problematic because few clinical trials evaluating therapy have been performed. A relatively large (n = 202) placebo-controlled, randomized trial[105] showed no benefit to using aspirin and prednisone in pregnant women with prior pregnancy losses and one or more autoantibodies (94 of 202 women [40%] had APLAs). Two randomized trials[106,107] compared aspirin and heparin to aspirin alone, and showed improved fetal survival with heparin and aspirin. Results of published case series[107a,107b] suggest that LMWH is efficacious in pregnant women with APLAs and fetal loss; currently, we and others are performing randomized trials evaluating the efficacy and safety of LMWH in pregnant women with APLAs. While available data suggest that aspirin and heparin is the regimen of choice for the prevention of pregnancy loss in pregnant women with APLAs and multiple previous pregnancy losses, it is likely that LMWH will also be effective. A more recent study,[45] however, found no difference in outcome

when these women were randomized to low-dose aspirin with LMWH or low-dose aspirin alone.

Pregnant women with APLAs (particularly "high-titer" anticardiolipin antibodies and/or lupus anticoagulants), no pregnancy losses, but previous venous thrombosis should be considered candidates for UFH or LMWH therapy, especially if they are already receiving long-term anticoagulant therapy. Women with APLAs and neither previous venous thrombosis nor pregnancy losses 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.

Recommendations

4.1. For women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death, we suggest screening for congenital thrombophilia and APLAs (**Grade 2C**).

4.2. For pregnant patients with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses, preeclampsia, IUGR, or abruption, we suggest administration of antepartum aspirin plus minidose or moderate-dose UFH or prophylactic LMWH (**Grade 2B**).

4.3. For women who are homozygous for thermolabile variant (C677T) of MTHFR, we suggest folic acid supplements prior to conception or, if already pregnant, as soon as possible, and throughout pregnancy (Grade 2C).

4.4. For women with a congenital thrombophilic deficit and recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abruption, we suggest low-dose aspirin therapy plus either minidose heparin or prophylactic LMWH therapy (**Grade 2C**). We also suggest that postpartum anticoagulants be administered to these women (**Grade 2C**).

4.5. Patients with APLAs and a history of venous thrombosis are usually receiving long-term oral anticoagulation therapy because of the high risk of recurrence. During pregnancy, we recommend adjusted-dose LMWH or UFH therapy plus low-dose aspirin and resumption of long-term oral anticoagulation therapy postpartum (**Grade 1C**).

4.6. Patients with APLAs and no prior VTE or pregnancy loss should be considered to have an increased risk for the development of venous thrombosis and, perhaps, pregnancy loss. We suggest one of the following approaches for these women: surveillance, minidose heparin, prophylactic LMWH, and/or low-dose aspirin, 75 to 162 mg/d (all **Grade 2C**).

5.0 Management of Pregnant Women With Prosthetic Heart Valves

Pregnant women with prosthetic heart valves pose a problem because of the lack of reliable data regarding the efficacy and safety of antithrombotic therapy during pregnancy. A retrospective survey[108] describing outcomes in pregnant women with mechanical heart valves concluded the following: warfarin was safe and not associated with embryopathy, and heparin was associated with more thromboembolic and bleeding complications than warfarin.

In order to examine the validity of these conclusions and explore optimum antithrombotic regimens, Chan and colleagues[109] performed a systematic review of the literature examining fetal and maternal outcomes of pregnant women with prosthetic heart valves. Since no randomized trials were identified, the overview consisted of prospective and retrospective cohort studies. Pooled estimates of maternal and fetal risks associated with the following three commonly used approaches were determined: (1) use of VKAs throughout pregnancy (in widespread use in Europe), (2) replacement of VKAs with UFH from 6 to 12 weeks, and (3) UFH use throughout pregnancy. In both VKA-containing regimens, heparin was commonly used close to term in order to avoid delivery of an anticoagulated fetus. Outcomes included pregnancy loss, fetopathic effects (including warfarin embryopathy), as well as maternal bleeding, thromboembolic complications, and death.

The use of VKAs throughout pregnancy was associated with warfarin embryopathy in 6.4% of live births (Table 4). The substitution of heparin at or prior to 6 weeks eliminated this risk. Overall the rates of fetal wastage (spontaneous loss, stillbirths, and neonatal deaths) were similar in the three groups. The overall pooled maternal mortality rate was 2.9% (Table 5). Major bleeding occurred in 2.5% of all pregnancies, mostly at the time of delivery (Table 6). The regimen associated with the lowest risk of valve thrombosis/systemic embolism (3.9%) was the use of VKAs throughout; using UFH only between 6 weeks and 12 weeks gestation was associated with an increased risk of valve thrombosis (9.2%) [Table 5].

This analysis suggests that VKAs are more efficacious than UFH for thromboembolic prophylaxis of women with mechanical heart valves in pregnancy; however, coumarins increase the risk of embryopathy. Substituting VKAs with heparin between 6 weeks and 12 weeks reduces the risk of fetopathic effects but possibly subjects the woman to an increased risk of thromboembolic complications. The reported high rates of thromboembolism with UFH might be explained by inadequate dosing and/or the use of an inappropriate target therapeutic range. The use of low-dose UFH is inadequate; the use of adjusted-dose UFH warrants aggressive monitoring and appropriate dose adjustment. Contemporary aPTT reagents are more sensitive to the anticoagulant effect of heparin; therefore, a minimum target aPTT ratio of 1.5 times the control is likely to be inadequate. A target aPTT ratio of at least twice the control should be attained.[110]

Reports of LMWH use in pregnant women with prosthetic heart valves are starting to appear,[111–117] and many physicians now use these agents during pregnancy in women with mechanical valves. Treatment failures have been reported,[114–117] and the use of LMWH for this indication has recently become controversial due to a warning from a LMWH manufacturer regarding their

Table 4—Frequency of Fetal Complications Reported With Various Anticoagulation Regimens*

Anticoagulation Regimen	Spontaneous Abortions	Congenital Fetal Anomalies	Fetal Wastage
VKAs throughout with/without heparin at term	196/792 (24.8)	35/549 (6.4)	266/792 (33.6)
Heparin in first trimester, then VKAs 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 from Chan et al,[109] and are presented as No./total (%).

safety in this situation.[118] This warning was based on an undisclosed number of postmarketing reports of thrombosed valves in patients receiving this LMWH, as well as the results of a very small randomized trial of pregnant women with prosthetic valves. In this study,[18] which was stopped after 12 patients were enrolled, pregnant women were randomized to receive either LMWH or UFH and warfarin administered sequentially. Although few details are available, according to the manufacturer, two of seven women treated with LMWH acquired valve thrombosis and outflow obstruction causing maternal and fetal deaths. Given the small numbers of patients enrolled in the study and the inability to determine accurate incidence rates from postmarketing data, the true incidence of valve thrombosis in pregnant women with mechanical valves treated with LMWH remains unknown.

All anticoagulant therapies used in this situation are associated with significant risks, but clearly, women with prosthetic heart valves require anticoagulation during pregnancy. Coumarins are contraindicated in pregnancy in North America due to fetal concerns. UFH has significant maternal side effects, and there are reports that it lacks efficacy, albeit when associated with doses of UFH that were likely to be inadequate. LMWH, with its good safety profile for mother and baby, should not be discarded in this situation until there are better comparative data. It is important to remember that the failures of UFH and LMWH reported in the literature do not exclude the possibility that these medications, if administered in high doses and aggressively monitored, would be effective.

To summarize, there are still insufficient grounds to make definitive recommendations about optimal antithrombotic therapy in pregnant patients with mechanical heart valves because properly designed studies have not been performed. Substantial concern remains about the fetal safety of warfarin, the efficacy of subcutaneous heparin and of LMWH in preventing thromboembolic complications, and the risks of maternal bleeding with various regimens. European experts have recommended warfarin therapy throughout pregnancy in view of the reports of bad maternal outcomes with heparin and their impression that the risk of embryopathy with coumarin

Table 5—Frequency of Maternal Complications Reported With Various Anticoagulation Regimens*

Anticoagulation Regimen	Thromboembolic Complications	Death (All Causes)	Comments
VKAs throughout, with/without heparin near term	31/788 (3.9)	10/561 (1.8)	8 cases of thromboembolic complications occurred on heparin (6 on IV or adjusted dose, 2 on low dose)
Heparin use in first trimester, then VKAs throughout with/without heparin near term	21/229 (9.2)	7/167 (4.2)	All 21 cases of thromboembolic complications 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 from Chan et al,[109] and are presented as No./total (%).

Table 6—Pooled Frequency of Bleeding Complications Reported From all Studies of Pregnant Women With Prosthetic Valves (Irrespective of Antithrombotic Regimen)*

Major Bleeding	Women, No.	Comments
Occurring at delivery	25	11 women were receiving IV or adjusted-dose heparin, 14 were receiving warfarin, and 6 were unknown.
Occurring outside of delivery	6	
Total	31	
Percentage of all pregnancies	2.5%	

*Data are from Chan et al.[109]

derivatives has been overstated.[108] Although this latter approach is reasonable, it is fraught with medicolegal concerns, because the package insert states that warfarin is contraindicated during pregnancy. We believe that warfarin should be avoided between 6 weeks and 12 weeks of gestation (to avoid embryopathy) and close to term (to avoid delivery of an anticoagulated fetus). Although the risks associated with warfarin during the remainder of pregnancy have been considered smaller, the recent association with neurodevelopment problems with mid-pregnancy exposure must also be considered.[40]

It appears reasonable to use one of the following three regimens: (1) either LMWH or UFH between 6 weeks and 12 weeks and close to term only, and to use VKAs at other times (despite medicolegal concerns); (2) aggressive dose-adjusted UFH throughout pregnancy; or (3) aggressive adjusted-dose LMWH throughout pregnancy. Before any of these approaches is used, it is crucial to explain the risks carefully to the patient. If warfarin is used, the dose should be adjusted to attain a target INR of 3.0 (range, 2.5 to 3.5); a lower therapeutic range of 2.0 to 3.0 can be used in patients with bileaflet aortic valves, provided they do not have atrial fibrillation or left ventricular dysfunction. If used, SC UFH should be initiated in high doses (17,500 to 20,000 U q12h) and adjusted to prolong a 6-h postinjection aPTT into the therapeutic range; strong efforts should be made to ensure an adequate anticoagulant effect. Adjusted-dose LMWHs are a reasonable substitute for UFH because they appear to reduce the risk of bleeding and osteoporosis and do not cross the placenta. Although further information is required about dosing for this indication, we recommend that LMWH be administered twice daily and dosed to achieve anti-Xa levels of 1.0 to 1.2 U/mL 4 to 6 h after SC injection. Extrapolating from data in nonpregnant patients with mechanical valves receiving warfarin therapy,[119] for some high-risk women, the addition of aspirin, 75 to 162 mg/d, can be considered in an attempt to reduce the risk of thrombosis, recognizing that it increases the risk of bleeding.

Recommendations

In women with prosthetic heart valves, we recommend:

5.1. Adjusted-dose bid LMWH throughout pregnancy in doses adjusted either to keep a 4-h postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight (**Grade 1C**), or

5.2. Aggressive adjusted-dose UFH throughout pregnancy, ie, administered SC q12h in doses adjusted to keep the mid-interval aPTT at least twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (**Grade 1C**), or

5.3. UFH or LMWH (as above) until the thirteenth week, change to warfarin until the middle of the third trimester, and then restart UFH or LMWH (**Grade 1C**).

Remark: Long-term anticoagulants should be resumed postpartum with all regimens.

5.4. In women with prosthetic heart valves at high risk, we suggest the addition of low-dose aspirin, 75 to 162 mg/d (**Grade 2C**).

Summary and Conclusions

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE, in patients with mechanical heart valves, and for the prevention of pregnancy complications in women with APLAs or hereditary thrombophilia and prior pregnancy complications.

VKAs are fetopathic, but the true risks of the warfarin embryopathy and CNS abnormalities remain unknown. There is considerable evidence that warfarin may not be fetopathic when administered in the first 6 weeks of gestation. Although there is considerable evidence that warfarin embryopathy occurs only when VKAs are administered between the sixth week and the twelfth week of gestation, concerns have been raised recently about long-term neurocognitive effects of warfarin on children exposed to during the mid-trimester of pregnancy. VKAs should be avoided in the weeks before delivery because of the risk of serious perinatal bleeding caused by the trauma of delivery to the anticoagulated fetus. The safety of aspirin during the first trimester of pregnancy is still a subject of debate. Although doubt has been raised about the effectiveness of heparin or LMWH for the prevention of systemic embolism in patients with mechanical heart valves, the observed failures could have been caused by inadequate dosing. Finally, the optimum management of pregnant women with thrombophilia (and prior pregnancy complications and/or prior VTE) is unknown, but trials of anticoagulant therapy are ongoing.

Summary of Recommendations

When describing the various regimens of UFH and LMWH, we will use the following short forms:
- Minidose UFH: UFH 5,000 U SC q12h
- Moderate-dose UFH: UFH SC q12h in doses adjusted to target an anti-Xa level of 0.1 to 0.3 U/mL.
- Adjusted-dose UFH: UFH SC q12h in doses adjusted to target a mid-interval aPTT into the therapeutic range.
- Prophylactic LMWH: *eg*, dalteparin 5,000 U SC q24h,

or enoxaparin 40 mg SC q24 h (although at extremes of body weight modification of dose may be required).

- Intermediate-dose LMWH: *eg*, dalteparin 5,000 U SC q12h, or enoxaparin 40 mg SC q12h.
- Adjusted-dose LMWH: weight-adjusted, full-treatment doses of LMWH administered 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 q12 h). As the half-life of LMWH is shorter in pregnancy, twice-daily dosing is preferable, at least in the initial treatment phase.
- Postpartum anticoagulants: warfarin 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.
- In addition, the term *surveillance* refers to clinical vigilance and aggressive investigation of women with symptoms suspicious of DVT or PE.

1.0 Management of Women Receiving Long-Term Vitamin K Antagonist Therapy Who Are Considering Pregnancy

1.1. For women requiring long-term VKA therapy who are attempting pregnancy, we suggest performing frequent pregnancy tests and substituting UFH or LMWH for warfarin when pregnancy is achieved (**Grade 2C**).

2.0 Treatment of VTE During Pregnancy

2.1. In women with acute VTE, we recommend either adjusted-dose LMWH throughout pregnancy or IV UFH (bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Anticoagulants should be administered for at least 6 weeks postpartum (**Grade 1C+**).

2.2. In women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuing the heparin 24 h prior to elective induction of labor (**Grade 1C**).

3.0 Prevention of VTE During Pregnancy

3.1 Prior VTE and pregnancy

3.1.1. In patients with a single episode of VTE associated with a transient risk factor that is no longer present, we recommend clinical surveillance and postpartum anticoagulants (**Grade 1C**). If the previous event is pregnancy or estrogen-related or there are additional risk factors (such as obesity), we suggest antenatal anticoagulant prophylaxis (**Grade 2C**).

3.1.2. In patients with a single idiopathic episode of VTE who are not receiving long-term anticoagulants, we suggest prophylactic LMWH, or minidose UFH, or moderate-dose UFH, or clinical surveillance plus postpartum anticoagulants (**Grade 2C**).

3.1.3. In patients with a single episode of VTE and thrombophilia (confirmed laboratory abnormality) or strong family history of thrombosis and not receiving long-term anticoagulants, we suggest prophylactic or intermediate-dose LMWH, or mini-dose or moderate-dose UFH, plus postpartum anticoagulants (**Grade 2C**).

3.1.4. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden and homozygotes for these conditions with a history of VTE, we suggest intermediate-dose LMWH prophylaxis or moderate-dose UFH (**Grade 2C**).

3.1.5. In patients with multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants (*eg*, single episode of VTE—either idiopathic or associated with thrombophilia) we suggest adjusted-dose UFH or adjusted-dose LMWH followed by resumption of long-term anticoagulants postpartum (**Grade 2C**).

3.1.6. In all women with previous DVT, antenatally and postpartum, we suggest use of graduated elastic compression stockings (**Grade 2C**).

3.2 Thrombophilia and venous thromboembolism associated with pregnancy

3.2.1. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden, and homozygotes for these conditions with no prior VTE, we suggest active prophylaxis (**Grade 2C**).

3.2.2. In all other patients with no prior VTE and thrombophilia (confirmed laboratory abnormality), we suggest surveillance or prophylactic LMWH or minidose UFH, plus postpartum anticoagulants (**Grade 2C**).

4.0 Thrombophilia and Pregnancy Complications

4.1. For women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death, we suggest screening for congenital thrombophilia and APLAs (**Grade 2C**).

4.2. For pregnant patients with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses, preeclampsia, IUGR, or abruption, we suggest administration of antepartum aspirin plus minidose or moderate-dose UFH or prophylactic LMWH (**Grade 2B**).

4.3. For women who are homozygous for thermolabile variant (C677T) of MTHFR, we suggest folic acid supplements prior to conception or, if already pregnant, as soon as possible, and throughout pregnancy (**Grade 2C**).

4.4. For women with a congenital thrombophilic deficit and recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abruption, we suggest low-dose aspirin therapy plus either minidose heparin or prophylactic LMWH therapy (**Grade 2C**). We also suggest that postpartum anticoagulants be administered to these women (**Grade 2C**).

4.5. Patients with APLAs and a history of venous thrombosis are usually receiving long-term oral anticoagulation therapy because of the high risk of recurrence.

During pregnancy, we recommend adjusted-dose LMWH or UFH therapy plus low-dose aspirin and resumption of long-term oral anticoagulation therapy postpartum (**Grade 1C**).

4.6. Patients with APLAs and no prior VTE or pregnancy loss should be considered to have an increased risk for the development of venous thrombosis and, perhaps, pregnancy loss. We suggest one of the following approaches for these women: surveillance, mini-dose heparin, prophylactic LMWH, and/or low-dose aspirin, 75 to 162 mg daily (**all Grade 2C**).

5.0 Prophylaxis in Patients with Mechanical Heart Valves

In women with prosthetic heart valves, we recommend:

5.1. Adjusted-dose, twice-daily LMWH throughout pregnancy in doses adjusted either to keep a 4-h postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight (**Grade 1C**), or

5.2. Aggressive adjusted-dose UFH throughout pregnancy: *ie*, administered SC q12h in doses adjusted to keep the mid-interval aPTT at least twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (**Grade 1C**), or

5.3. UFH or LMWH (as above) until the thirteenth week, change to warfarin until the middle of the third trimester, and then restart UFH or LMWH (**Grade 1C**).

Remark: Long-term anticoagulants should be resumed postpartum with all regimens.

5.4. In women with prosthetic heart valves at high risk, we suggest the addition of low-dose aspirin, 75 to 162 mg/d (**Grade 2C**).

References

1 The National Institute for Clinical Excellence, Scottish Executive Health Department and Department of Health, Social Services and Public Safety: Northern Ireland. Confidential Enquiries into Maternal Deaths in the United Kingdom 1997–99. London: TSO, 2001. Available at: http://www.cemach.org.uk/publications/CEMDreports/cemdrpt.pdfhttp://www.cemach.org.uk/publications/CEMDreports/cemdrpt.pdf. Accessed July 2003

2 Hull RD, Raskob GF, Carter CJ. Serial IPG in pregnancy patients with clinically suspected DVT: clinical validity of negative findings. Ann Intern Med 1990; 112:663–667

3 Hull RD, Hirsh J, Carter C, et al. Diagnostic efficacy of IPG for clinically suspected DVT: a randomized trial. Ann Intern Med 1985; 102:21–28

4 Hull RD, Hirsh J, Sackett D, et al. Diagnostic efficacy of IPG in suspected venous thrombosis: an alternative to venography. N Engl J Med 1977; 296:1497–1500

5 Lensing AWA, Prandoni P, Brandjes D, et al. Detection of DVT by real-time B-mode ultrasonography. N Engl J Med 1989; 320:342–345

6 Ginsberg JS, Kearon C, Douketis J, et al. D-dimer and impedance plethysmography in patients with suspected deep vein thrombosis: results of a management trial. Arch Intern Med 1997; 157:1077–1081

7 Chan WS, Ray JG, Murray S, et al. Suspected pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes Arch Intern Med 2002; 162:1170–1175

8 PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263:2753–2759

9 Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985; 88:819–828

10 Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scot Med J 1996; 41:83–86

11 Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999; 353:1258–1265

12 Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. Thromb Haemost 1992; 67:519–520

13 Cockett FB, Thomas ML, Negus D. Iliac vein compression: its relation to iliofemoral thrombosis and the post-thrombotic syndrome. BMJ 1967; 2:14–16

14 Hunt BJ, Doughty HA, Majumdar G, et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. Thromb Haemost 1997; 77:39–43

15 Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997; 176:1062–1068

16 Blomback M, Bremme K, Hellgren M, et al. Thromboprophylaxis with low molecular mass heparin, "Fragmin" (dalteparin), during pregnancy: longitudinal safety study. Blood Coagul Fibrinolysis 1998; 9:1–9

17 Blomback M, Bremme K, Hellgren M, et al. A pharmacokinetic study of dalteparin during late pregnancy. Blood Coagul Fibrinolysis 1998; 9:343–350

18 Brennand JE, Walker ID, Greer IA. Anti-activated factor X profiles in pregnant women receiving antenatal thromboprophylaxis with enoxaparin. Acta Haematol 1999; 101:53–55

19 Dulitzki M, Pauzner R, Langevitz P, et al. Low molecular weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol 1996; 87:380–383

20 Casele HL, Laifer SA, Woelkers DA, et al. Changes in the pharmacokinetics of the low molecular weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol 1999; 181:1113–1117

21 Ellison J, Walker ID, Greer IA. Antifactor Xa profiles in pregnant women receiving antenatal thromboprophylaxis with enoxaparin for prevention and treatment of thromboembolism in pregnancy. Br J Obstet Gynaecol 2000; 107:1116–1121

22 Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. Br J Obstet Gynaecol 2001; 108:1134–1140

23 Dolovich L, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low molecular weight heparins to unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160:181–188

24 Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130:800–809

25 de Valek HW, Banga JD, Wester JWJ, et al. Comparing subcutaneous danaparoid with intravenous unfractionated heparin for the treatment of venous thromboembolism: a randomized controlled trial. Ann Intern Med 1995; 123:1–9

26 Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopedic surgery: a meta-analysis. Lancet 1992; 340: 152–156

27 Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337:688–698

28 Nelson-Piercy C, Letsky EA, et al. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997; 176:1062–1068

29 Forestier F, Daffos F, Capella-Pavlovsky M. Low molecular weight heparin (PK 10169) does not cross the placenta during the second trimester of pregnancy: study by direct fetal blood sampling under ultrasound. Thromb Res 1984; 34:557–560

30 Forestier F, Daffos F, Rainaut M, et al. Low molecular weight heparin (CY 216) does not cross the placenta during the third trimester of pregnancy [letter]. Thromb Haemost 1987; 57:234

31 Sanson BJ, Lensing AWA, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost 1999; 81:668–672

32 Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335

33 Monreal M, Lafoz E, Olive A, et al. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications for coumarin. Thromb Haemost 1994; 71:7–11

34 Pettila V, Leinonen P, Markkola A, et al. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 2002; 87:182–186

35 Mora A, Belch J, Contreras L, et al. Delayed-type hypersensitivity skin reactions to low molecular weight heparins in a pregnant woman. Contact Dermatitis 2002; 47:177–178

36 Flessa HC, Klapstrom AB, Glueck MJ, et al. Placental transport of heparin. Am J Obstet Gynecol 1965; 93:570–573

37 Ginsberg JS, Hirsh J, Turner CD, et al. Risks to the fetus of anticoagulant therapy during pregnancy. Thromb Haemost 1989; 61:197–203

38 Ginsberg JS, Kowalchuk G, Hirsh J, et al. Heparin therapy during pregnancy: Risks to the fetus and mother. Arch Intern Med 1989; 149:2233–2236

39 Hall JAG, Paul RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy Am J Med 1980; 68:122–140

40 Wesseling J, van Driel D, Heymans HAS, et al. Coumarins during pregnancy: long term effects on growth and development in school age children. Thromb Haemost 2001; 85:609–613

41 Hull RD, Delmore TJ, Carter CJ, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med 1982; 306:189–194

42 Hull RD, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982; 307:1676–1681

43 Chunilal SD, Young E, Johnston MA, et al. The aPTT response of pregnant plasma to unfractionated heparin. Thromb Haemost 2000; 87:92–97

44 Anderson DR, Ginsberg JS, Burrows R, et al. Subcutaneous heparin therapy during pregnancy: a need for concern at the time of delivery. Thromb Haemost 1991; 63:248–250

45 Farquarson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomised controlled trial of treatment. Obstet Gynecol 2002; 100:408–413

46 Magnani HN. Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with Orgaran (Org 10172). Thromb Haemost 1993; 70:554–561

47 Douketis JD, Ginsberg JS, Burrows RF, et al. The effects of long-term heparin therapy during pregnancy on bone density. Thromb Haemost 1996; 75:254–257

48 Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 1993; 168:1265–1270

49 Muir J, Andrew M, Hirsh J, et al. Histomorphometric analysis of the effects of standard heparin on trabecular bone *in vivo*. Blood 1996; 88:1314–1320

50 Shaughnessy SG, Hirsh J, Bhandari M, et al. Histomorphometric evaluation of heparin-induced bone loss after discontinuation of heparin treatment in rats. Blood 1999; 93:1231–1236

51 Muir JM, Hirsh J, Weitz JI, et al. A histomorphometric comparison of the effects of heparin and low-molecular-weight heparin on cancellous bone in rats. Blood 1997; 89:3236–3242

52 O'Reilly R. Anticoagulant, antithrombotic and thrombolytic drugs. In: Gillman AG, Goodman LS, Gilman A, eds. The pharmacologic basis of therapeutics, 6th ed. New York, NY: Macmillan, 1980; 1347

53 Orme L'E, Lewis M, de Swiet M, et al. May mothers given warfarin breast-feed their infants? BMJ 1977; 1:1564–1565

54 McKenna R, Cole ER, Vasan V. Is warfarin sodium contraindicated in the lactating mother? J Pediatr 1983; 103:325–327

55 Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for prevention of pregnancy-induced hypertensive disease. JAMA 1991; 266:260–264

56 CLASP Collaborative Group. CLASP: a randomised trial of low dose aspirin for the prevention and treatment of pre-eclampsia among 9,364 pregnant women. Lancet 1994; 343:619–629

57 Lopaciuk S, Bilska-Falda H, Noszczyk W, et al. Low-molecular-weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thromb Haemost 1999; 81:26–31

58 Pini M, Aiello S, Manotti C, et al. Low-molecular-weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost 1994; 72:191–197

59 van der Heijden JF, Hutten BA, Buller HR, et al. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. Cochrane Database Syst Rev 2000(4):CD002001

60 Crowther MA, Spitzer K, Julian J, et al. Pharmacokinetic profile of a low-molecular weight (Reviparin) in pregnant patients: a prospective cohort study. Thromb Res 2000; 98:133–138

61 Rodie VA, Thomson AJ, Stewart FM, et al. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: case series. Br J Obstet Gynaecol 2002; 109:1020–1024

62 Thomson AJ, Greer, IA. Thromboembolic disease in pregnancy and the puerperium: acute management. Royal College of Obstetricians and Gynaecologists, London. Guideline No 20, 2001. Available at: http:www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=20). Accessed July 2003

63 Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–153

64 De Swiet M, Floyd E, Letsky E. Low risk of recurrent thromboembolism in pregnancy [letter]. Br J Hosp Med 1987; 38:264

65 Howell R, Fidler J, Letsky E, et al. The risk of antenatal subcutaneous heparin prophylaxis: a controlled trial. Br J Obstet Gynecol 1983; 90:1124–1128

66 Badaracco MA, Vessey M. Recurrent venous thromboembolic disease and use of oral contraceptives. BMJ 1974; 1:215–217

67 Tengborn L. Recurrent thromboembolism in pregnancy and puerperium: is there a need for thromboprophylaxis? Am J Obstet Gynecol 1989; 160:90–94

68 Brill-Edwards P, Ginsberg JS, for the Recurrence Of Clot In This Pregnancy (ROCIT) Study Group. Safety of withholding antepartum heparin in women with a previous episode of venous thromboembolism. N Engl J Med 2000; 343:1439–1444

69 Pettila V, Kaaja R, Leinonen P, et al. Thromboprophylaxis with low-molecular-weight heparin "dalteparin" in pregnancy. Thromb Res 1999; 96:275–282

70 Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. N Engl J Med 1988; 318:1162–1173

71 Gerhardt A, Scharf RE, Beckman MW, et al. Prothrombin and factor V mutations in women with thrombosis during pregnancy and the puerperium. N Engl J Med 2000; 342:374–380

72 McColl M, Ramsay JE, Tait RC, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997; 8:1183–1188

73 McColl MD, Ellison J, Reid F, et al. Prothrombin 20210GA, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. Br J Obstet Gynaecol 2000; 107:567–569

74 Martinelli I, de Stefano V, Taioli E, et al. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost 2002; 87:791–795

75 Friederich PW, Sanson B-J, Simioni P, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med 1996; 125:955–960

76 Long AA, Ginsberg JS, Brill-Edwards P, et al. The relationship of antiphospholipid antibodies to thromboembolic disease in systemic lupus erythematosus: a cross-sectional study. Thromb Haemost 1991; 66:520–524

77 Middledorp S, Van der Meer J, Hamulyak K, et al. Counselling women with factor V Leiden homozygosity: use absolute instead of relative risks. Thromb Haemost 2001; 87:360–361

78 Middledorp S, Libourel EJ, Hamulyak K, et al. The risk of pregnancy-related venous thromboembolism in women who are homozygous for factor V Leiden. Br J Haematol 2001; 113:553–555

79 Martinelli I, Legnani C, Bucciarelli P, et al. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001; 86:800–803

80 Pabinger I, Nemes L, Rintelen C, et al. Pregnancy-associated risk for venous thromboembolism and pregnancy outcome in women homozygous for factor V Leiden. Hematol J 2000; 1:37–41

81 Den Heijer M, Rosendaal FR, Blom HJ, et al. Hyperhomocysteinemia as a risk for deep-vein thrombosis. N Engl J Med 1995; 334:759–762

82 Grandone E, Margaglione M, Colaizzo D, et al. Genetic susceptibility to pregnancy-related venous thromboembolism: roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. Am J Obstet Gynecol 1998; 179:1324–1328

83 Greer IA. The challenge of thrombophilia in maternal-fetal medicine. N Engl J Med 2000; 342:424–425

84 Report of the RCOG Working Party on prophylaxis against thromboembolism in gynaecology and obstetrics. London, UK: Royal College of Obstetricians and Gynaecologists, 1995

85 Hague WM, North RA, Gallus AS, et al. Anticoagulation in pregnancy and the puerperium. Med J Aust 2001; 175:258–263

86 Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period (Cochrane Review). Cochrane Database Syst Rev. 2002; (2):CD001689

87 Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 341:9–13

88 Nelen WL, Steegers EA, Eskes TK, et al. Genetic risk factor for unexplained recurrent early pregnancy loss [letter]. Lancet 1997; 350:861

89 Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348:913–916

90 Sanson BJ, Friederich PW, Simioni P, et al. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost 1996; 75:387–388

91 Murphy RP, Donoghue C, Nallen RJ. Prospective evaluation of the risk conferred by Factor V Leiden and thermolabile methylenetetrahydrofolate reductase polymorphisms in pregnancy. Arterioscler Thromb Vasc Biol 2000; 20:266–270

92 Younis JS, Brenner B, Ohel G. Activated protein C resistance and factor V Leiden mutation can be associated with first as well as second trimester recurrent pregnancy loss. Am J Reprod Immunol 2000; 43:31–35

93 Gris JC, Quere I, Monpeyroux F, et al. Case-control study of the frequency of thrombophilic disorders in couples with late fetal loss and no thrombotic antecedent: the Nimes Obstetricians and Haematologists Study 5(NOHA5). Thromb Haemost 1999; 81:891–899

94 Martinelli JR, Taioli E, Cetin I, et al. Mutations in coagulation factors in women with unexplained late fetal loss. N Engl J Med 2000; 343:1015–1018

95 Rai R, Shlebak A, Cohen H, et al. Factor V Leiden and acquired activated protein C resistance among 1000 women with recurrent miscarriage. Hum Reprod 2001; 16:961–965

96 Pihusch R, Buchholz T, Lohse P, et al. Thrombophilic gene mutations and recurrent spontaneous abortion: prothrombin mutation increases the risk in the first trimester. Am J Reprod Immunol 2001; 46:124–131

97 Reznikoff-Etievan MF, Cayol V, Carbonne B, et al. Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. Br J Obstet Gynaecol 2001; 108:1251–1254

98 Nelen WL, Blom HJ, Steegers EA, et al. Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. Fertil Steril 2000; 74:1196–1199

99 Rey E, Kahn SR, David M, et al. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003; 361:901–908

100 Alferivic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome. Eur J Obstet Gyencol Reprod Biol 2002; 101:6–14

101 Morrison ER, Miedzybrodzka ZH, Campbell D, et al.

Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. Thromb Haemost 2002; 87:779–785

102 Infante-Rivard C, Rivard GE, Wagner VYH, et al. Absence of association of thrombophilic polymorphism with intra-uterine growth restriction. N Engl J Med 2002; 347:19–25

103 Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Ann Intern Med 1990; 112:682–698

104 Ginsberg JS, Brill-Edwards P, Johnston M, et al. Relationship of antiphospholipid antibodies to pregnancy loss in patients with systemic lupus erythematosus: a cross-sectional study. Blood 1992; 80:975–980

105 Laskin CA, Bombardier C, Hannah ME, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. N Engl J Med 1997; 337:148–153

106 Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997; 314:253–257

107 Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 1996; 174:1584–1589

107a Lima F, Khamashta MA, Buchananans, et al. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumatol 1996; 14:131–136

107b Backos M, Rai R, Baxter N, et al. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. Br J Obstet Gynaecol 1999; 106:102–107

108 Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J 1994; 71:196–201

109 Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000; 160:191–196

110 Brill-Edwards P, Ginsberg JS, Johnston M, et al. Establishing a therapeutic range for heparin. Ann Intern Med 1993; 119:104–109

111 Arnaout MS, Kazma H, Khalil A, et al. Is there a safe anticoagulation protocol for pregnant women with prosthetic valves? Clin Exp Obstet Gynecol 1998; 25:101–104

112 Lee LH, Liauw PC, Ng AS. Low molecular weight heparin for thromboprophylaxis during pregnancy in 2 patients with mechanical mitral valve replacement [letter]. Thromb Haemost 1996; 76:628–630

113 Rowan JA, McCowan LM, Raudkivi PJ, et al. Enoxaparin treatment in women with mechanical heart valves during pregnancy. Am J Obstet Gynecol 2001; 185:633–637

114 Roberts N, Ross D, Flint SK, et al. Thromboembolism in pregnant women with mechanical prosthetic heart valves anticoagulated with low molecular weight heparin. Br J Obstet Gynaecol 2001; 108:327–329

115 Leyh RG, Fischer S, Ruhparwar A, et al. Anticoagulation for prosthetic heart valves during pregnancy: is low-molecular-weight heparin an alternative. Eur J Cardiothorac Surg 2002; 21:577–579

116 Mahesh B, Evans S, Bryan AJ. Failure of low molecular-weight heparin in the prevention of prosthetic mitral valve thrombosis during pregnancy: case report and review of options for anticoagulation. J Heart Valve Dis 2002; 11:745–750

117 Lev-Ran O, Kramer A, Gurevitch J, et al. Low-molecular-weight heparin for prosthetic heart valves: treatment failure. Ann Thorac Surg 2000; 69:264–265

118 Lovenox Injection (package insert). Bridgewater, NJ: Aventis Pharmaceuticals, 2004

119 Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med 1993; 329:524–529