Use of Antithrombotic Agents During Pregnancy

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Abbreviations: APLA = antiphospholipid antibody; APTT = activated partial thromboplastin time; CI = confidence interval; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IUGR = intrauterine growth restriction; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; s/c = subcutaneous; UHF = unfractionated heparin; VTE = venous thromboembolism

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Fatal pulmonary embolism (PE) remains a common cause of maternal mortality. Maternal mortality from PE can be reduced in two ways: (1) by aggressively investigating symptomatic women when they present with a clinical suspicion of deep vein thrombosis (DVT) or PE; and (2) by treatment and/or prophylaxis in women who have an increased risk for DVT and/or PE. Both approaches are problematic for several reasons. The first approach is problematic because nonthrombotic symptoms that mimic DVT and PE are common during pregnancy, the tests used to diagnose DVT can be altered by the compressive effects of the gravid uterus on the iliac veins, and there is a concern about performing procedures (such as lung scanning) that expose the fetus to radiation. The second approach is problematic because prophylaxis or treatment of DVT and PE involves long-term parenteral unfractionated heparin (UHF) or low-molecular-weight heparin (LMWH); both are inconvenient, painful, expensive, and associated with a risk of bleeding, osteoporosis, and heparin-induced thrombocytopenia (HIT), although these complications are probably less frequent with LMWH than UHF. Appropriate management of pregnant women with prior venous thromboembolism (VTE) is problematic because, until recently, reliable information on the true incidence of recurrence in such women was not available. Furthermore, many women with prior VTE have an identifiable abnormality associated with thrombophilia, and the management of such individuals is controversial.

Since our last review, new information has been published on the management of pregnant women with previous VTE, the safety and pharmacokinetics of LMWH during pregnancy, the mechanisms of osteoporosis caused by UHF and LMWH, the problems of managing pregnant women with prothrombotic risk factors, 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.

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Epidemiology of VTE During Pregnancy

The true incidence of VTE associated with pregnancy is unknown, but there is strong clinical impression that the risk is increased compared to the incidence in nonpregnant individuals. Available evidence suggests that the risk of VTE is higher after cesarean section (particularly emergency cesarean section) than after vaginal delivery. 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%), 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. A relatively greater proportion of thrombi during pregnancy are in the iliofemoral veins, where they are more likely to embolize.

Although the clinical diagnosis of VTE during pregnancy is inaccurate, the nonspecificity is compounded by the facts that leg swelling and pain (mimicking DVT) and chest pain and dyspnea (mimicking PE) are common during pregnancy and are usually nonthrombotic in origin. In support of this, the prevalence of DVT in a study of consecutive pregnant patients presenting with a clinical suspicion was <10, compared to approximately 25% in studies of nonpregnant populations whereas a recent study (W.S. Chan; unpublished data) found that only 2 of 50 subjects (4%) with suspected PE had the disease, compared to about 30% of nonpregnant patients who presented with suspected PE.

Thrombophilia and Pregnancy

There are two main adverse experiences that are associated with thrombophilia and pregnancy. These are (1) VTE and (2) pregnancy complications associated with placental infarction, including miscarriage, IUGR, preeclampsia, abruptio, and intrauterine death. Friederich et al have shown that asymptomatic women with congenital deficiencies of antithrombin, protein C, or protein S have approximately an eightfold increased risk of VTE during pregnancy compared to normal control subjects. Howevet, in absolute terms, the risk of VTE was relatively low (7 of 169 pregnancies; 4.1%). Two of these episodes occurred during the third trimester, and the remaining five occurred postpartum. In addition, one study has shown that 60% of women who develop VTE during pregnancy have factor V Leiden. Other thrombophilic disorders, such as the prothrombin gene mutation, hyperhomocysteinemia, and persistent antiphospholipid antibodies (APLAs), are probably also associated with an increased risk of VTE during pregnancy and the puerperium. There is a clinical impression as well as retrospective data suggesting that antithrombin deficiency imparts a higher risk of VTE than other thrombophilias. Accordingly, such women should be treated more aggressively than those with other inherited thrombophilias.

During pregnancy, 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; in the study cited above, < 2% of women with antithrombin, protein C, or
protein S deficiency suffered VTE during pregnancy. 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.

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%. 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 overestimate of the frequency of recurrence. Antepartum heparin therapy 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 given in the postpartum period for 4 to 6 weeks. The antepartum recurrence rate was 2.4% (95% confidence interval [CI], 0.2 to 6.9%). Ninety-five patients had 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, the absolute risk of antepartum recurrent VTE in women without thrombophilia and whose previous episode of thrombosis was associated with a temporary risk factor is low and antepartum heparin prophylaxis is not routinely justified. Further studies are needed to determine whether prophylaxis is warranted in patients with thrombophilia by laboratory testing and/or a previous episode of idiopathic thrombosis.

Repeated screening with noninvasive tests for DVT, such as compression ultrasound, is not justified for two reasons in these patients because, even with a sensitivity of 96% and a specificity of 98%, the positive predictive value of compression ultrasound would be only 10% if we postulate that the prevalence of recurrent VTE is about 5%. Second, the timing of screening with ultrasound is problematic. Even if performed as often as weekly, a woman could still develop clinically important recurrence 2 to 3 days after normal ultrasound findings. Therefore, we are modifying our previous recommendation that women at risk for VTE should be screened routinely with regular noninvasive tests, with the recommendation that they should be investigated aggressively if symptoms suspicious of DVT or PE occur.

**Thrombophilia and Pregnancy Loss**

Maternal thrombophilias are now recognized to be associated with pregnancy complications, including fetal loss, IUGR, preeclampsia, abruption, and intrauterine death.

With regard to miscarriage, several case-control studies have shown a relationship between factor V Leiden and second trimester miscarriage. However, in contrast to APLA syndrome, there are no reliable data at present (and to our knowledge) to link the congenital thrombophilias with first trimester loss. Interestingly, hyperhomocysteinemia has been associated with early pregnancy loss. It has been postulated that first trimester miscarriage reflects the failure of implantation while second trimester miscarriage reflects thrombotic events in the placenta.

There is also an association between stillbirth and thrombophilia, particularly with antithrombin deficiency, but also with combined defects. The stillbirths may reflect an increase in the pregnancy complications of IUGR, preeclampsia, and abruption. The main relationships appears to be with hyperhomocysteinemia, factor V Leiden, and the prothrombin gene variant.

In view of these data, women with recurrent pregnancy loss, including at least one second trimester miscarriage, or a history of intrauterine death or severe or recurrent preeclampsia or growth restriction, 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 have been shown to be effective in reducing miscarriage rates, we have no data to indicate whether such antithrombotic therapy is beneficial. Nevertheless, since many of these women are at risk of VTE, antithrombotic therapy should be considered. Although hyperhomocysteinemia has not been associated with DVT in pregnancy, hyperhomocysteinemia and reduced serum folic acid concentrations are risk factors for recurrent spontaneous miscarriage; therefore, folic acid supplementation may be beneficial in such patients.

**APLAs**

APLAs can be detected using clotting assays (lupus anticoagulant) or immunoassays (anticardiolipin antibodies) and have been reported to occur in systemic lupus erythematosus with use of certain drugs and in apparently healthy individuals. There is convincing evidence that the presence of APLAs is associated with an increased risk of thrombosis and pregnancy loss. 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 APLA prior to or during the early part of pregnancy. The management of pregnant women with APLA is problematic because few clinical trials evaluating therapy have been performed. A relatively large (n = 202), placebo-controlled, randomized trial showed no benefit to using...
aspirin and prednisone in pregnant women with prior pregnancy losses and one or more autoantibodies; 94 of 202 women (46.5%) had APLAs. Two randomized trials compared aspirin and heparin to aspirin alone and showed improved fetal survival with heparin and aspirin.42-43 Results of published case series suggest that LMWH is efficacious in pregnant women with APLAs and fetal loss. Currently, we and others are evaluating the efficacy and safety of LMWHs in randomized trials in women with APLAs. The available data suggest that aspirin and heparin therapy 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 LMWHs will also be effective.

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. 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 treated either with careful clinical surveillance for VTE or prophylactic UFH or LMWH.

**Anticoagulant Therapy During Pregnancy**

The anticoagulants currently available for the prevention and treatment of VTE and arterial thromboembolism include heparin and heparin-like compounds (UFH, LMWH, and heparinoids), coumarin derivatives, as well as 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.

**LMWHs and Heparinoids**

There is accumulating experience with the use of these agents both in pregnant and nonpregnant patients for the prevention and treatment of DVT.34-40 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 DVT41,42 and for the prevention of DVT in patients who undergo surgery.43 LMWHs have the advantage of a longer plasma half-life and a more predictable dose response than UFH.44 There is also evidence that LMWH (and heparinoids) do not cross the placenta.35,46,47 and a recent overview48 concluded that LMWH was safe for the fetus. These agents have potential advantages over UFH during pregnancy because they cause less HIT,49 have the potential for once-daily administration, and probably result in a lower risk of heparin-induced osteoporosis.30

**Dose Regimens of LMWH**

LMWHs are more expensive than UFH, but given the advantages listed above, the clear-cut evidence of their efficacy in nonpregnant patients, and the fact that they are safe for the fetus, they are suitable for routine clinical use in pregnant patients who require anticoagulant therapy. 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. As the pregnancy progresses (and most women gain weight), the volume of distribution for LMWH changes. Therefore, two options are available. The first is to simply change the dose in proportion to the weight change.51 The second is to perform weekly anti-factor Xa levels 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. For prophylaxis of VTE, several dose regimens and LMWHs have been used. Common regimens that have been reported in case series, small cohort studies, and one randomized trial52 include subcutaneous (s/c) dalteparin, 5,000 U q24h34; enoxaparin, 40 mg q24h39,40; and dose-adjusted LMWH to achieve a peak anti-Xa level of 0.2 to 0.6 U/mL.34,36 Although all of the studies reported low recurrence rates, none was a placebo-controlled trial; therefore, the recurrence rates might have been low without prophylaxis. LMWH should also be considered in patients with intractable painful skin reactions to UFH and in those with osteopenia.

**Fetal Complications of Anticoagulants During Pregnancy**

There are two potential fetal complications of maternal anticoagulant therapy: teratogenicity and bleeding. Neither UFH53 nor LMWH54,46,47 cross the placenta and therefore do not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible. Three studies strongly suggest that UFH/LMWH therapy is safe for the fetus.45,54,55

In contrast to heparin, coumarin derivatives cross the placenta and have the potential to cause both bleeding in the fetus and teratogenicity.56,57 Coumarin derivatives can cause an embryopathy, which consists of nasal hypoplasia and/or stippled epiphyses, after in utero exposure to oral anticoagulants during the first trimester of pregnancy, and CNS abnormalities, which can occur after exposure to such drugs during any trimester.56 It is probable that oral anticoagulants 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.58 In addition, these oral anticoagulants cause an anticoagulant 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,55 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 patients59 and with warfarin therapy60 when used for the treatment of DVT. In addition, adjusted-dose s/c UFH can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use prior to labor.61 In a small study, an anticoagulant effect persisted for up to 28 h after the last injection of adjusted-dose s/c heparin, frequently resulting in deliveries that were complicated by a pro-
longed activated partial thromboplastin time (APTT). The mechanism for this prolonged effect is unclear; however, one way to avoid an unwanted anticoagulant effect during delivery in women receiving adjusted-dose s/c UFH therapy is to discontinue the heparin therapy 24 h prior to elective induction of labor. If spontaneous labor occurs in women receiving adjusted-dose s/c UFH, careful monitoring of the APTT (or heparin level) is required and, if it is prolonged near delivery, protamine sulfate may be required to reduce the risk of bleeding. It is important to recognize that during pregnancy, the APTT response to heparin is often attenuated because of increased levels of factor VIII and fibrinogen. This may mislead the clinician into falsely concluding that there is no heparin activity present because the APTT level can be normal with significantly elevated heparin levels. Bleeding complications appear to be very uncommon with LMWH. Nevertheless, near term, we suggest the same approach to women receiving “treatment doses” of LMWH as in those receiving adjusted-dose UFH, namely discontinuing LMWH therapy 24 h prior to elective induction of labor.

**Immune HIT**

Approximately 3% of nonpregnant patients receiving UFH develop immune, IgG-mediated thrombocytopenia, which is frequently complicated by extension of preexisting VTE or new arterial thrombosis. This should be differentiated from an early, benign, transient thrombocytopenia that can occur with initiation of UFH therapy. 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 × 10^9/L or < 50% of the baseline value 5 to 15 days after commencing heparin therapy, or sooner with recent heparin exposure.

In pregnant women who develop HIT and require ongoing anticoagulant therapy, use of the heparinoid, danaparoid sodium, is recommended because it is an effective antithrombotic agent and has much less cross-reactivity with UFH and, therefore, less potential to produce recurrent HIT than LMWH.

**Heparin-Induced Osteoporosis**

Long-term heparin therapy has been reported to cause osteoporosis in both laboratory animals and humans. 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 about 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 therapy. Dahlman 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 reported spinal fractures in 6 of 40 patients (15%) receiving s/c UFH, 10,000 IU bid, for a period of 3 to 6 months. The reason for the higher incidence of osteoporotic fractures (15% vs 2%) is probably due to the fact that the patients in the study by Monreal et al were significantly older than those in the study by Dahlman.

Recently, Shaughnessy and associates performed a series of studies in Sprague Dawley rats and other experimental models that provided new information on the mechanism of heparin-induced osteoporosis. In one study, animals treated with UFH at doses ranging from 0.25 to 1.0 anti-Xa U/g for 28 days showed a dose-dependent decrease in cancellous bone volume in the distal third of the femur. They were also able to show that UFH causes bone loss by decreasing rates of bone formation while at the same time increasing rates of bone resorption.

In a second study, designed to determine whether the effects of UFH on bone are reversible, rats were randomized to once-daily s/c injections of either UFH or saline solution for 28 days and then followed up for an additional 28 days without treatment. Heparin caused a 30% loss in cancellous bone volume over the first 28 days. To explore the mechanism for the prolonged effect of heparin on bone, the experiment was repeated using 125I-labeled heparin instead of unlabeled heparin. 125I-labeled heparin accumulated in bone during the course of its administration and was retained in bone for at least 28 days after stopping heparin treatment. These findings suggest that heparin-induced osteoporosis is not rapidly reversible because heparin is sequestered in bone for extended periods.

Several lines of evidence now suggest that LMWHs have a lower risk of osteoporosis than heparin. In the study by Monreal et al, dalteparin, 5,000 IU anti-Xa bid s/c, was compared with UFH, 10,000 IU bid s/c, in 80 patients with VTE; both treatments were administered for a period of 3 to 6 months. Six of the 40 patients (15%) who received UFH developed spinal fractures compared with only 1 of 40 patients (2.5%) receiving dalteparin. Studies using an animal model of heparin-induced osteoporosis support the hypothesis that LMWHs cause less osteoporosis than UFH. Thus, when rats were treated with once daily s/c injections of UFH, 1.0 U/g or 0.5 U/g, or the 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 given to nursing mothers. There have been two convincing reports 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 safe and these women 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. The results of a meta-analysis and a large (> 9,000 patients) randomized trial 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 intranerine growth retardation was safe for the mother and fetus because no increase in maternal or neonatal adverse effects occurred in individuals treated with aspirin. Thus, based on current evidence, low-dose aspirin (<150 mg/d) during the second and third trimesters appears to be safe, but the safety of higher doses of aspirin and/or aspirin ingestion during the first trimester remains uncertain.

Efficacy of Anticoagulants for the Prevention and Treatment of VTE During Pregnancy

There is a paucity of data about the efficacy of anticoagulants for the prevention and treatment of VTE during pregnancy. Accordingly, the 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. Based on the safety data, a heparin-related compound (LMWH or UFH) is the drug of choice for the prevention and treatment of VTE during pregnancy. There are now many well-designed randomized trials and meta-analyses comparing IV UFH and s/c LMWH for the treatment of acute DVT and PE. They show that LMWH is at least as safe and effective as UFH. There are also studies in nonpregnant patients showing that long-term LMWH (and UFH) are as effective and safe as warfarin for the prevention of recurrent VTE. In view of the totality of the data, we endorse the use of LMWH for initial and long-term treatment of acute VTE. Two alternative approaches are reasonable: IV UFH followed by at least 3 months of s/c heparin, in doses adjusted to prolong a mid-interval APTT into the therapeutic range (adjusted-dose s/c heparin); or adjusted-dose s/c heparin can be used both for initial and long-term treatment.

Prophylaxis of VTE in Pregnant Women With Thrombophilia

When evaluating women who are deemed to have an increased risk of VTE, several issues must be addressed. The first is to critically evaluate the evidence that the women indeed have VTE and/or thrombophilia. Once this is done, based on laboratory and clinical data, women can be 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 anticoagulation therapy; (3) single episode of VTE and thrombophilia (confirmed laboratory abnormality) and not receiving long-term anticoagulation therapy; (4) no prior VTE and thrombophilia (confirmed laboratory abnormality); or (5) multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulation therapy (eg, single episode of VTE, either idiopathic or associated with thrombophilia).

These are broad categories, and the 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 treated more aggressively if she required bed rest or was morbidly obese.

Based on the currently available studies, there are two general approaches to pregnant patients with previous VTE: (1) active prophylaxis with UFH or LMWH; and (2) clinical surveillance. Several cohort studies and one randomized trial have reported low recurrence rates with the use of prophylactic once-daily LMWH treatment.44 – 58 Given the added convenience of LMWH and decreased HIT and osteoporosis, it is becoming the preferred choice. Alternatively, UFH, 5,000 U s/c q12h, is effective and safe for the prevention of VTE in high-risk nonpregnant patients,75 and its use has been recommended in pregnant patients. However, there is a concern that a dose of heparin, 5,000 U s/c q12h, may be insufficient in high-risk situations because it does not reliably produce detectable heparin levels. There are also published data75 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. Until comparative studies are performed, it is impossible to make definitive recommendations about which regimen to use for prophylaxis (if active prophylaxis rather than clinical surveillance is chosen).

Management of Pregnant Women With Prosthetic Heart Valves

Pregnant women with prosthetic heart valves pose problems because of the lack of reliable data on the efficacy and safety of antithrombotic therapy during pregnancy. A retrospective survey by Sharouni and Oakley of outcomes in pregnant women with mechanical heart valves concluded (1) that warfarin was safe and not associated with embroyopathy, and (2) that 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 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) oral anticoagulants throughout pregnancy (in widespread use in Europe); (2) replacing oral anticoagulants with UFH from 6 to 12 weeks; and (3) UFH use throughout pregnancy. In both warfarin-containing regimens, heparin was usually used close to term in order to avoid delivery of an anticoagulated fetus. Outcomes included pregnancy loss and fetopathic effects (including warfarin embroyopathy), as well as maternal bleeding, thromboembolic complications, and death.

The use of oral anticoagulants throughout pregnancy was associated with warfarin embroyopathy in 6.4% of live births (Table 1). 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 2). Major bleeding occurred in 2.5% of all pregnancies, mostly at the time
of delivery (Table 3). The regimen associated with the lowest risk of valve thrombosis/systemic embolism (3.9%) was the use of oral anticoagulants throughout; using UFH only between 6 weeks and 12 weeks gestation was associated with an increased risk of valve thrombosis (9.2%; Table 2). This analysis suggests that oral anticoagulants are more efficacious than UFH for thromboembolic prophylaxis of women with mechanical heart valves in pregnancy; however, coumarins increase the risk of embryopathy. Substituting oral anticoagulants 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 use of low-dose UFH is inadequate; the use of adjusted-dose UFH warrants aggressive monitoring and appropriate dose adjustment. The need for a large prospective study to determine the best regimen for pregnant women with mechanical valves is clear.

Although the reported high rates of thromboembolism with UFH might be explained by inadequate dosing and/or the use of an inappropriate target therapeutic range, this overview does raise the concern that patients with mechanical heart valves are resistant to moderate doses of UFH and draws attention to the need to use adequate heparin doses in these patients. Insufficient heparin dosing is associated with treatment failure, emphasizing the need for adequate initial heparinization and stringent monitoring. 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. Finally, reports of LMWH use in pregnant women with prosthetic heart valves are starting to appear. They might ultimately have a definitive role for this indication.

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 s/c heparin in preventing thromboembolic complications, and the risks of maternal bleeding with various regimens. We believe

<table>
<thead>
<tr>
<th>Anticoagulation Regimen</th>
<th>Spontaneous Abortions</th>
<th>Congenital Fetal Anomalies</th>
<th>Fetal Wastage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA throughout with/without heparin at term</td>
<td>196/792 (24.8%)</td>
<td>35/549 (6.4%)</td>
<td>266/792 (33.6%)</td>
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<tr>
<td>Heparin used at/before 6 wk</td>
<td>19/129 (14.7)</td>
<td>0/108 (0.0)</td>
<td>21/129 (16.3)</td>
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<td>Heparin use after 6 wk</td>
<td>19/56 (33.9)</td>
<td>4/36 (11.1)</td>
<td>20/56 (35.7)</td>
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<td>Heparin used at unknown time in first trimester</td>
<td>19/45 (42.2)</td>
<td>2/30 (6.7)</td>
<td>20/45 (44.4)</td>
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<td>Total</td>
<td>57/230 (24.8)</td>
<td>6/174 (3.5)</td>
<td>61/230 (26.5)</td>
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<tr>
<th>Anticoagulation Regimen</th>
<th>Death (All Causes)</th>
<th>*Comments</th>
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<tbody>
<tr>
<td>OA throughout, with/without heparin near term</td>
<td>31/788 (3.9)</td>
<td>Eight cases of TEC occurred with heparin (six receiving IV or adjusted dose; two on low-dose)</td>
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<tr>
<td>Heparin used in first trimester, then OA throughout with/out heparin near term</td>
<td>21/229 (9.2)</td>
<td>All 21 cases of TEC occurred with heparin (10 receiving IV or adjusted dose; 10 on low-dose; dose unknown in 1 case)</td>
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<tr>
<td>Heparin throughout</td>
<td>4/16 (25.0)</td>
<td>1/15 (6.7)</td>
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<td>Low-dose heparin</td>
<td>3/5 (60.0)</td>
<td>2/5 (40.0)</td>
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<td>Total</td>
<td>7/21 (33.3)</td>
<td>3/20 (15.0)</td>
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<td>Total</td>
<td>26/107 (24.3)</td>
<td>5/106 (4.7)</td>
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</table>

*Data are presented as No./patients (%); OA = oral anticoagulants.
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), but is probably safe at other times. We believe it is reasonable to use LMWH or UFH either during these periods only, combined with warfarin with a target INR of 3.0 (range, 2.5 to 3.5; range, 2.0 to 3.0 in patients with a bileaflet aortic valve provided they do not have atrial fibrillation or left ventricular dysfunction) at other times, or to use UFH or LMWH throughout pregnancy. In addition, European experts have recommended warfarin therapy throughout pregnancy in view of the reports of bad outcomes with heparin and the impression that the risk of embryopathy with coumarin derivatives has been overstated. Although this latter approach is reasonable, it is fraught with medicolegal concerns, because the package insert states that warfarin is contraindicated during pregnancy. Before this approach is used, it is crucial to explain the risks carefully to women. If used, s/c UFH therapy 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, since inadequate doses of heparin are ineffective. LMWH is probably a reasonable substitute for UFH because it seems to reduce the risk of bleeding and osteoporosis and does not cross the placenta, but further information is required about dosing for this indication. In addition, for some high-risk patients, aspirin, 80 mg daily, can be considered in an attempt to reduce the risk of thrombosis, recognizing that it increases the risk of bleeding.

**SUMMARY AND CONCLUSIONS**

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 loss in women with APLAs or thrombophilia and previous pregnancy losses. Several questions concerning anticoagulant therapy remain unanswered. It appears that LMWH will largely replace UFH. Oral anticoagulants are fetopathic, but the true risks of the warfarin embryopathy and CNS abnormalities remain unknown. There is considerable evidence that warfarin embryopathy occurs only when oral anticoagulants are administered between the sixth week and the 12th week of gestation and that oral anticoagulants may not be fetopathic when administered in the first 6 weeks of gestation. Oral anticoagulant therapy 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. There is a concern about the efficacy of UFH in the prevention of arterial embolism in pregnant women with mechanical heart valves. Finally, the optimum management of pregnant women with thrombophilia (and prior pregnancy loss and/or prior VTE) is unknown, but trials of anticoagulant therapy are ongoing.

Because it is safe for the fetus, LMWH (or UFH) is the anticoagulant of choice during pregnancy for situations in which its efficacy is established. There is some doubt that heparin is effective for the prevention of systemic embolism in patients with mechanical heart valves. Low doses of heparin or poorly controlled heparin therapy are not effective in preventing systemic embolism in patients with mechanical heart valves.

**RecommenDations**

When describing the various regimens of UFH and LMWH, we will use the following terminology: 1. *mini-dose* UFH (UFH, 5,000 U s/c q12h); 2. *moderate-dose* UFH (UFH s/c every 12 h in doses adjusted to target an anti-Xa level of 0.1 to 0.3 U/mL); 3. *adjusted-dose* UFH (UFH s/c every 12 h in doses adjusted to target a mid-interval APTT into the therapeutic range); 4. prophylactic LMWH (either dalteparin, 5,000 U s/c q24h, or enoxaparin, 40 mg s/c q24h, or any once-daily LMWH adjusted to target a peak anti-Xa level of 0.2 to 0.6 U/mL); 5. adjusted-dose LMWH (weight-adjusted, full-treatment doses of LMWH; for example, dalteparin, 200 U/kg q24h, or enoxaparin, 1 mg/kg q12h); 6. 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.

**Management of Pregnant Patients at Increased Risk for VTE**

1. For single episode of prior VTE associated with a transient risk factor (and no additional current risk factors, such as morbid obesity or strict bed rest), surveillance and postpartum anticoagulants. This is a grade 1C recommendation.
2. For single episode of idiopathic VTE in patients not receiving long-term anticoagulation therapy, surveillance or mini-dose UFH or moderate-dose UFH or prophylactic LMWH, plus postpartum anticoagulants. This is a grade 1C recommendation.
3. For single episode of VTE and thrombophilia (confirmed laboratory abnormality) in patients not receiving long-term anticoagulation therapy, surveil-
lance or mini-dose UFH or moderate-dose UFH or prophylactic LMWH, plus postpartum anticoagulants. The indication for active prophylaxis is stronger in antithrombin-deficient women than the other thrombophilias. This is a grade 1C recommendation.

(4) For no prior VTE and thrombophilia (confirmed laboratory abnormality), surveillance or mini-dose UFH or prophylactic LMWH, plus postpartum anticoagulants. The indication for active prophylaxis is stronger in antithrombin-deficient women than the other thrombophilias. This is a grade 1C recommendation.

(5) For multiple (more than two) episodes of VTE, and/or women receiving long-term anticoagulation therapy (eg, single episode of VTE, either idiopathic or associated with thrombophilia), adjusted-dose UFH or either prophylactic or adjusted-dose LMWH, followed by resumption of long-term anticoagulation therapy postpartum. This is a grade 1C recommendation.

Treatment of VTE of Pregnancy

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 for the remainder of the pregnancy. To avoid an unwanted anticoagulant effect during delivery in women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuing the heparin therapy 24 h prior to elective induction of labor. If the woman is deemed to have a very high risk of recurrent VTE (eg, proximal DVT within 2 weeks), therapeutic IV UFH therapy can be initiated and discontinued 4 to 6 h prior to the expected time of delivery. Postpartum anticoagulation therapy should be administered for at least 6 weeks. This is a grade 1C recommendation.

Unexpected Pregnancy or Planned Pregnancy in Patients Who Are Receiving Long-term Anticoagulation Therapy

If possible, such women should be counseled about the risks before pregnancy occurs. If pregnancy is still desired, two options can be considered:

(1) Perform frequent pregnancy tests and substitute adjusted-dose UFH or LMWH for warfarin when pregnancy is achieved; or

(2) Replace warfarin with UFH or LMWH before conception is attempted. Both approaches have limitations; the first approach assumes that warfarin is safe during the first 4 to 6 weeks of gestation; the second approach increases the duration of exposure to heparin and, therefore, to a higher risk of osteoporosis. We favor the first approach because it is convenient and appears to be safe. These are grade 1C recommendations.

Prophylaxis in Patients With Mechanical Heart Valves

One of three approaches is recommended:

(1) Aggressive adjusted-dose UFH therapy through-

out pregnancy (ie, administered s/c every 12 h in doses adjusted to keep the mid-interval APTT at least twice the control, or an anti-Xa heparin level of 0.35 to 0.70 U/mL). This is a grade 2C recommendation;

(2) Adjusted-dose LMWH therapy throughout pregnancy in doses adjusted according to weight or to keep a 4-h postinjection anti-Xa heparin level at approximately 1.0 U/mL. This is a grade 2C recommendation; or

(3) UFH or LMWH (as above) therapy until the 13th week, a change to warfarin until the middle of the third trimester, and then restart UFH or LMWH therapy until delivery. This is a grade 2C recommendation.

Long-term anticoagulation therapy should be resumed postpartum with all regimens.

Management of Pregnant Women at Increased Risk for Pregnancy Loss

(1) Women with recurrent pregnancy loss (three or more miscarriages) should be screened for APLAs. If the losses include one or more second-trimester losses, screening for congenital thrombophilia should be performed. Women with prior severe or recurrent preeclampsia, IUGR, abruption, or otherwise unexplained intrauterine death should be screened for congenital thrombophilia and APLAs.

(2) Pregnant patients with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses or preeclampsia, IUGR, or abruption should be treated with antepartum aspirin plus mini-dose or moderate-dose UFH or prophylactic LMWH. This is a grade 1B recommendation.

(3) Women found to be homozygous for thermolabile variant (C677T) of methylenetetrahydrofolate reductase should be treated with folic acid supplements prior to conception or, if already pregnant, as soon as possible. This is a grade 2C recommendation.

(4) Women with a thrombophilic deficit and (A) recurrent miscarriages, (B) a second-trimester or later loss, or (C) preeclampsia, IUGR, or abruption should be considered for low-dose aspirin therapy plus either mini-dose heparin or prophylactic LMWH therapy. We also administer postpartum anticoagulants to these women. These are grade 2C recommendations.

(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 throughout pregnancy and resumption of long-term oral anticoagulation therapy postpartum. This is a grade 2C recommendation.

(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 recommend one of four approaches: surveillance, mini-dose heparin, prophylactic LMWH, or low-dose aspirin, 80 to 325 mg qd. This is a grade 2C recommendation.
REFERENCES

40 CASEL E HL, Laifer SA, Woelkers DA, et al. Changes in the pharmacokinetics of the low molecular weight heparin enox-
45 Deleted in proof.
46 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
62 Chumil SD, Young E, Johnston M, et al. Comparison of the nonspecific binding of a low molecular weight heparin (Dalteparin) with unfractionated heparin in pregnant and non-pregnant plasma [abstract]. Thromb Haemost 1999; (suppl):532
63 Magnani HN. Heparin-induced thrombocytopenia (HIT); an overview of 230 patients treated with Orgaran (Org 10172). Thromb Haemost 1993; 70:354–361
76 Sharomi E, Oakley CM. Outcome of pregnancy in women with valve prosthesis. Br Heart J 1994; 71:196–201