

OBSTETRICS

Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes

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The incidence of pregnancy-related venous thromboembolism (VTE) is difficult to measure. The common symptoms and signs are nonspecific—dyspnea, tachypnea, peripheral edema, and leg pain—and are often associated with advanced, normal pregnancy, sometimes making the diagnosis difficult. Even when VTE is suspected, some practitioners are reluctant to use diagnostic tests because of fears of radiation exposure to the fetus. Consequently, the occurrence of VTE is probably underestimated in pregnant patients. Despite these difficulties, the incidence of VTE in pregnancy is reported to be 4- to 6-fold higher than in age-matched nonpregnant women,^{1,2} and pulmonary embolism (PE) remains a frequent cause of maternal mortality.^{2,3} Indeed, VTE is the

Venous thromboembolism and adverse pregnancy outcomes are potential complications of pregnancy. Numerous studies have evaluated both the risk factors for and the prevention and management of these outcomes in pregnant patients. This consensus group was convened to provide concise recommendations, based on the currently available literature, regarding the use of antithrombotic therapy in pregnant patients at risk for venous thromboembolic events and adverse pregnancy outcomes.

Key words: pregnancy, thrombophilia, venous thromboembolism

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leading cause of maternal death in both the United Kingdom and North America, with death from PE occurring in 2 in 100,000 deliveries in the United Kingdom⁴ and representing 11% of maternal deaths in the United States.⁵ Women

who experience DVT during pregnancy are also more likely to have poor pregnancy outcomes. Furthermore, the risk of VTE extends to the postpartum period, with 50% of VTE cases occurring postpartum.⁶

After a firm diagnosis of VTE has been made in the pregnant patient, the perceived complications of antithrombotic therapy sometimes delay or inhibit its implementation. A pregnant patient's risk of having VTE develop is difficult to estimate and is dependent on numerous factors, some not readily identifiable by clinical history or examination. As a result, identifying the patient who would benefit from prophylaxis is difficult. A number of publications have addressed these problems, and some guidelines for prevention and treatment of VTE have been issued.⁷⁻¹⁰ However, these guidelines are incomplete and are not always evidence based. The major reason for this deficiency is the relative paucity of well-designed, properly powered, randomized controlled trials in prevention and treatment of thromboembolism associated with pregnancy.

To define current consensus on these issues an expert meeting was organized by

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TABLE 1
Grading of evidence according to the US Preventive Services Task Force¹¹

Grade of evidence	
I	Evidence obtained from at least 1 properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Recommendation	
A	Recommendation is based on good and consistent scientific evidence.
B	Recommendation is based on limited or inconsistent scientific evidence.
C	Recommendation is based primarily on consensus and expert opinion.

Aventis Pharmaceuticals, a member of the Sanofi-Aventis group. In subgroups, 6 topics were discussed, including identification of the problem, risk assessment, options of prevention and counseling for VTE, options of prevention and counseling for poor obstetric history, practical management of anticoagulation and pregnancy, and anticoagulation in labor, postpartum and beyond. A round-table discussion of all topics by all participants followed, from which an original outline resulted. Based on the outline, this report was drafted, refined, and agreed on after multiple review rounds after the meeting was held. The working group maintained full and independent responsibility for content of the consensus document.

This report provides a concise update for practitioners in maternal and fetal health. Recommendations for the use of antithrombotic drugs in pregnancy are given throughout the report. Recommendation grades A to C and evidence levels I to III are based on the US Preventive Services Task Force grading of evidence (Table 1).¹¹ In brief, grade A recommendations and level I evidence come from randomized controlled trials with clear results; grade B recommendations and level II evidence come from well-designed non-randomized studies with limited or inconsistent evidence; and level III evidence and grade C recommendations result from consensus opinions of respected experts and authorities based on clinical experience and descriptive studies.

PHARMACOLOGIC MANAGEMENT OF VTE IN PREGNANCY

Management of thrombosis in pregnancy remains a challenge. The anticoagulant drugs currently available for the prevention and treatment of VTE include warfarin, unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), factor-Xa inhibitors, and direct thrombin inhibitors.

Warfarin, a coumarin derivative, interacts with many other medications. Because of the physiologic changes associated with pregnancy as well as nausea and vomiting, it is difficult to attain stable anticoagulation with this drug. Use of the drug during the first trimester has been associated with spontaneous abortion and warfarin embryopathy, consisting of mental retardation, optic atrophy, microphthalmia, cataracts, ventral midline dysplasia, nasal hypoplasia, stippled bones and epiphyses, and central nervous system (CNS) abnormalities in approximately 4-5% of exposed fetuses. Frequencies of abnormalities up to 29% have been reported in patients requiring warfarin for mechanical heart valves.¹²⁻¹⁴ Moreover, warfarin can cause CNS abnormalities after exposure at any stage during pregnancy. Warfarin readily crosses the placenta and results in fetal anticoagulation that is not readily reversible, resulting in an increased risk of intracranial hemorrhage.¹⁵ Warfarin

is minimally secreted into the breast milk and is therefore considered safe to use in breastfeeding mothers.^{7,16} Treatment guidelines recommend postpartum anticoagulation with warfarin for 4-6 weeks with a target international normalized ratio (INR) of 2.0-3.0 (with overlap with UFH or LMWH until the INR \geq 2.0).⁷

UFH has a short half-life and must be administered subcutaneously or via continuous infusion.¹⁷ The current treatment guidelines recommend subcutaneous dosing of UFH every 12 hours; either as a low dose of 5000 U, to achieve target anti-Xa between 0.1 and 0.3 U/mL (moderate dosing), or to achieve target midinterval aPTT into the therapeutic range (adjusted dosing).⁷ It requires frequent laboratory monitoring and dosage adjustment. Although UFH can be reversed by protamine sulfate, its use is complicated by the potential for bleeding complications (probably due to its effect on factor IIa resulting in inhibition of prothrombin activity and an anticoagulant effect). Although heparin-induced thrombocytopenia (HIT) is infrequently reported in pregnancy, it remains a concern, as up to 5% of individuals treated with standard heparin develop this complication, which is associated with a high thrombosis risk. Long-term use of UFH has been reported to cause osteoporosis, which is a concern in patients who require treatment throughout their pregnancy.¹⁷ UFH is classified by the Food and Drug Administration (FDA) as a

pregnancy category C drug. It does not cross the placenta and is considered safe for the fetus when used during pregnancy. UFH is not secreted in breast milk and can be used by nursing mothers.⁷

LMWHs are administered subcutaneously either once or twice daily for the prevention or treatment of VTE. They have considerable theoretical benefits over UFH, including better bioavailability,^{18,19} longer plasma half-life (or higher anti-factor-Xa activity),²⁰ more predictable pharmacokinetics and pharmacodynamics,²¹ less potential to cause osteoporosis,²² and lower incidence of HIT.²³ LMWHs inhibit factor Xa more effectively than factor IIa to produce their antithrombotic effect.²⁴ Many data are available supporting the use of LMWH over UFH for the treatment of acute VTE in nonpregnant patients,²⁵ and monitoring anticoagulation intensity or dosage adjustments are generally unnecessary with LMWH in these populations. However, pregnant patients can present an exception to this rule because the pharmacokinetics of LMWHs can change during pregnancy.⁷ The increased renal clearance and changes in maternal weight over the course of pregnancy may necessitate higher and more frequent dosing than in the nonpregnant individual. LMWHs are cleared from the body partially via a nonsaturable (renal) route of elimination.²⁶ Pregnancy is characterized by initial increase in glomerular filtration rate with a subsequent decrement at term. Protamine only reverses the anti-IIa activity of LMWH completely, whereas the anti-Xa activity is not fully neutralized (maximum reversal ~60%).²⁶ LMWHs are classified by the FDA as a pregnancy category B drug. They do not cross the placenta and are safe for the fetus.^{7,27} LMWHs are not secreted in breast milk and can therefore be safely used by nursing mothers.⁷ The safety profile of LMWHs has been further confirmed in a recent systematic review encompassing 64 reports on 2777 patients.²⁸ Furthermore, a recent study confirmed that consistent administration of LMWH during both the acute and long-term therapy for VTE during pregnancy was associated with lower rates of adverse events compared with 3

other comparator regimens containing UFH (intravenous [IV] UFH followed by LMWH, IV UFH, followed by subcutaneous [SC] UFH and SC UFH). The lower incidence of adverse events resulted in lower overall treatment costs for the LMWH regimen.²⁹

Factor-Xa inhibitors are a relatively new class of anticoagulants. Fondaparinux became the first drug in this class to gain FDA approval for the prevention of VTE in major orthopedic surgery and for the treatment of acute VTE. Fondaparinux is labeled as a pregnancy category B drug. Animal reproduction studies have demonstrated no harm to the fetus or to fertility, although fondaparinux was found to be secreted in breast milk in these studies.³⁰ No adequate clinical data exist on the use of fondaparinux in pregnant women.³⁰

Several direct thrombin inhibitors are approved for clinical use in the United States. Lepirudin, bivalirudin, and argatroban are labeled by the FDA as pregnancy category B drugs.³¹⁻³³ Animal studies have demonstrated no evidence of impaired fertility or harm to the fetus. However, animal studies have shown that lepirudin can cross the placenta³¹ and argatroban has been detected in breast milk.³² It is not known, definitively, whether these drugs are secreted in human breast milk. Currently there are no adequate clinical data on the use of direct thrombin inhibitors in pregnant women.

RISK ASSESSMENT

The hemostasis changes in pregnancy that tend to create a prothrombotic milieu have been well documented.³⁴⁻⁴² Pregnancy is associated with a 20-200% increase in levels of fibrinogen and factors II, VII, VIII, X, and XII.⁴³ Decreases occur in both the natural anticoagulation system, such as decreases in protein S levels,⁴¹ and in the fibrinolytic process, evidenced by increases in plasminogen-activator inhibitor 1 (PAI-1) and 2 (PAI-2)⁴⁴ and thrombin-activatable fibrinolysis inhibitor (TAFI) levels.⁴⁵

IDENTIFICATION OF PATIENTS AT RISK OF VTE

Potential candidates for anticoagulation in pregnancy can be classified as patients

who require anticoagulation for maternal indications, and those who require anticoagulation for the prevention of adverse pregnancy outcomes (APOs). Pregnant women may have more than 1 indication for anticoagulation since the underlying medical illness may predispose to APOs that may be amenable to anticoagulant therapy.

Maternal thromboembolism

1.1 History of VTE. The risk of VTE in pregnancy ranges from 0.05% to 1.8%, with a rate of recurrent VTE of 1.4-11.1%.⁴⁶⁻⁴⁸ Levels of coagulation activation markers such as prothrombin fragment 1.2 (PF1.2) and thrombin-antithrombin complex (TAT) increase with the progression of pregnancy to levels seen in patients with active thrombosis.⁴⁹ Therefore, women in the later stages of pregnancy often require an increase in the dose of UFH to maintain therapeutic levels of anticoagulation.⁵⁰

Brill-Edwards et al⁴⁶ addressed the safety of withholding heparin treatment in 125 pregnant women with a history of VTE occurring more than 3 months before the current pregnancy. An antepartum recurrence of VTE occurred in 2.4% of these patients. No recurrences occurred in the 44 women without evidence of thrombophilia or with a temporary risk factor associated with the previous episode, whereas 5.9% of 51 patients with thrombophilia or an idiopathic VTE had an antepartum recurrence. A subsequent study by Pabinger et al⁵¹ also found that the risk of symptomatic VTE recurrence was 3-fold higher during pregnancy, but that temporary risk factors (such as trauma, surgery or immobilization) at the first event did not differentiate clearly between women at high risk or low risk of a pregnancy-associated VTE recurrence. These data suggest that not all pregnant women with a previous VTE need be treated with prophylactic anticoagulants. They also indicate that the presence of thrombophilia or previous idiopathic VTE is a risk factor for VTE.

1.2 Inherited thrombophilic conditions. Inherited thrombophilias are a heterogeneous group of disorders in-

TABLE 2
Thrombophilia and thromboembolism¹

Inherited thrombophilia	General incidence	VT or VTE	VT/VTE in pregnancy or puerperium
AT deficiency (most thrombogenic)	0.02-0.17% 1% in patients with VTE	50% life chance of VTE	50% chance VTE in pregnancy
APCR or factor V Leiden*	3-7% of white women	Incidence of 20-30% with VTE	APCR found in 78% with VTE Factor V Leiden in 46% with VTE (predictive value 1:500)
Protein S or C deficiency [†]	0.14-0.5%	Found in 3.2% with VTE	Protein S 0-6% Protein C 3-10% Postpartum: Protein S 7-22% Protein C 7-19%
Factor V Leiden and PGM G20210A			Predictive value 4.6:100 Prevalence in VTE 9.3% vs 0 in control group
Hyperhomocysteinemia/homozygous MTHFR (C677T/A1298C)	8-10% of healthy population	Increased risk	NA

APCR, activated protein C resistance; NA, not available; PGM, prothrombin gene mutation; VT, venous thrombosis.

* Includes causes other than factor V Leiden for resistance to APC.

[†] Protein S levels decrease in pregnancy to below normal standard reference range.

cluding deficiencies of protein S, protein C, and antithrombin (AT). In 1994, an association between a mutation in the factor V gene and increased thrombotic risk was first reported.⁵² This mutation is present in 5% of American white, 1% of African American, and 5-9% of European populations, but is rare in Asian and African populations.^{53,54} The factor V mutation is associated with resistance to activated protein C (APC) and is inherited primarily in an autosomal-dominant fashion.^{54,55} Heterozygosity is found in 20-40% of nonpregnant patients with thromboembolic disease, whereas homozygosity confers a more than 100-fold increased risk of thromboembolic disease.⁵⁴ More recently, the prothrombin gene mutation (prothrombin G20210A) has been found to increase circulating prothrombin levels⁴⁸ and hence the risk of both thrombosis⁵⁰ and pregnancy complications.⁵⁶ In women with a history of VTE during pregnancy, prothrombin G20210A was found in 17% of patients compared with 1% of age-matched controls.⁵⁷ Homozygosity for prothrombin G20210A is thought to confer an equivalent risk of VTE to that of factor V Leiden homozygosity.⁵⁸

Other inherited thrombophilic mutations, including methylene tetrahydrofolate reductase (MTHFR) C677T and A1298C (often associated with hyperhomocysteinemia) and PAI gene mutations 4G/4G, 4G/5G, and 5G/5G, have been weakly associated with pregnancy complications.⁵⁹⁻⁶¹ The MTHFR mutations have been associated with neural tube defects, and other malformations.

Data from several studies suggest that abnormalities in the natural anticoagulation system, such as AT deficiency, APC resistance, and protein S or C deficiency, induce varying degrees of increased risk for thrombosis in pregnancy and the puerperium (Table 2).^{1,57,62-65} Although heterozygous factor V Leiden and prothrombin G20210A have lower hazard ratios for thrombosis, they are by far the most commonly noted mutations associated with thrombosis and adverse outcomes in pregnancy.^{49,66-68}

1.3 Obesity. Obesity has been associated with higher risk of atherothrombotic disease and VTE in the general medical population.⁶⁹ Multiple aspects of obesity aggravate the prothrombotic risk in pregnancy. The fibrinolytic process is decreased, as manifest by increased levels of PAI-1, PAI-2,⁷⁰ and

TAFI.⁴⁵ There is a high incidence of insulin-resistance syndrome (also known as metabolic syndrome or syndrome X) in obese patients. A core feature of this syndrome is elevated plasma levels of PAI-1,⁷¹ the primary inhibitor of both tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), which limits the fibrinolytic process.⁷⁰ Low-dose aspirin reduces plasma levels of PAI-1 in pregnant patients.⁷²

Data from several studies indicate adverse outcomes associated with obesity in pregnant women.^{73,74} The combination of pregnancy and obesity would logically be considered a compounded hypercoagulable and prothrombotic state. Sebire et al⁷³ studied 287,213 singleton pregnancies. Compared with women with normal body mass index (BMI 20-24.9 kg/m²), obese women (BMI > 25 kg/m²) were significantly more likely to develop gestational diabetes mellitus and proteinuric preeclampsia, to have induced labor, to undergo emergency cesarean delivery, and to experience postpartum hemorrhage, genital tract infection, urinary infection, wound infection, birth weight greater than the 90th per-

TABLE 3
Clinical risk factors for VTE (ORs with CIs)

	Lindqvist et al ³⁷ (N = 603)	Danilenko-Dixon et al ⁷⁷ (N = 90)	Anderson and Spencer ⁷⁸ (N = 1231)
Moderate-risk factors			
Age ≥ 35 y	1.3 (1-1.7)		2.0 (age > 40 y)
Parity			
2	1.5 (1.1-1.9)	1.1 (0.9-1.4)	
≥ 3	2.4 (1.8-3.1)		
Smoking	1.4 (1.1-1.9)	2.5 (1.3-4.7)	
Multiple gestation	1.8 (1.1-3.0)	7 (0.4-135.5)	
Preeclampsia	2.9 (2.1-3.9)	1 (0.14-7.1)	
Varicose veins		2.4 (1.04-5.4)	4.5
Obesity		1.5 (0.7-3.2)	< 2
Cesarean section	3.6 (3.0-4.3)		
Obstetric hemorrhage		9 (1.1-71.0)	
High-risk factors			
Spinal cord injury			> 10
Major abdominal surgery ≥ 30 min			> 10

centile, and intrauterine death. This population of patients may benefit from screening for common thrombophilic mutations such as factor V Leiden, prothrombin G20210A, MTHFR C677T/A1298C, as well as functional protein S and C, and AT deficiency, although few data currently exist as to the benefit of screening in obese patients. Further studies are necessary to determine whether this population should be screened. The risk-benefit ratio of prescribing heparin or low-dose aspirin to high-risk obese patients who have not had a VTE requires further investigation.

1.4. Surgery. Pregnancy adds an additional hypercoagulable state to the thrombotic risks associated with surgery. In general the risk of fatal PE is 0.2-0.9% in patients undergoing elective surgery.⁷⁵ Risk factors include advanced age, a history of VTE, obesity, heart failure, paralysis, or thrombophilia.⁷⁵ Surgical risk has been classified into the following 3 categories:⁷⁵

1. Low risk: Patients under the age of 40 years, no additional risk factors, and undergoing minor procedure.

2. Moderate risk: Patients undergoing a minor procedure with general anesthesia for more than 30 minutes and are 40-60 years old or have additional risk factors. Patients younger than 40 years with no additional risk factors and undergoing major surgery.

3. High risk: Patients older than 40 years or with additional risk factors undergoing major surgery. Patients undergoing minor surgery who are older than 60 years or have additional risk factors.

1.5 Family history. As many thrombophilic states are inherited, patients with a family history of VTE may be at increased risk for VTE. The risk is further increased in the presence of thrombophilic conditions. Specifically, the risk is increased approximately 8-fold for AT deficiency, 7-fold for protein C deficiency, and doubled for factor V Leiden mutation.⁷⁶

1.6. Other risk factors. Bed rest is often recommended to pregnant women with threatened preterm labor, preeclampsia, and/or signs of uteroplacental insufficiency. However, this involves

prolonged immobilization, which is known to be a risk factor for VTE in the absence of pregnancy. Therefore, prolonged bed rest under these conditions may also place pregnant women at a higher risk of VTE. Furthermore, other moderate risk factors should also be considered including age older than 35 years, smoking, multiple gestation, and preeclampsia, as outlined in Table 3.^{37,77,78}

2. Adverse pregnancy outcomes. After excluding congenital birth defects and idiopathic preterm delivery, severe preeclampsia at 36 weeks or less, intrauterine growth retardation (IUGR), fetal loss at 20 weeks' gestation or more, and abruption account for three-quarters of all cases of fetal mortality and/or morbidity, with a prevalence of approximately 8% (Table 4).⁷⁹

Numerous studies examining the association between inherited thrombophilias and adverse reproductive outcomes have been performed. However, there are no clear conclusions to be drawn from these studies, as some show a positive relationship between thrombophilias and adverse outcomes, whereas others show no association.

TABLE 4
Prevalence and risk of recurrence of APO without thrombophilia

Previous pregnancy complication	Prevalence of pregnancy complication (%)	Pregnancy complication in subsequent pregnancy (%)	Fetal death with pregnancy complication (%)
Fetal loss after or at 20 wks	0.5	8.5	8.5
Severe preeclampsia	2	26	13.5
HELLP	1	4	13.5
Eclampsia	0.5	3	13.5
Abruption	0.8	5	26
IUGR \leq 5th percentile	5.3	16	20
One or more	8	61-85	—

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Some of the most widely quoted studies demonstrating a positive association are flawed by the small number of patients or the use of composite outcomes.^{56,80} Systematic reviews have evaluated the association between factor V Leiden or the prothrombin gene mutation G20210A and IUGR.⁸¹⁻⁸³ Both mutations confer an increased risk of giving birth to a growth-restricted infant (factor V Leiden: odds ratio [OR] 2.7, 95% CI 1.3-5.5; prothrombin G20210A mutation: OR 2.5, 95% CI 1.3-5.5), but the association may be driven by small studies of poor quality that demonstrated extreme associations.⁸¹

Several studies, most of which were case controlled, have examined the relation between heterozygous factor V Leiden and severe preeclampsia.^{56,80,83-93} Factor V Leiden was identified in between 5% and 26% of patients with severe preeclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).^{56,84-87,93-95} In a systematic review of 18 preeclampsia studies,⁸² a positive association between factor V Leiden and preeclampsia or eclampsia (OR 1.6, 95% CI, 1.2-2.1) was found.

In the largest study published to date involving women whose infants had IUGR (defined as $<$ 10th percentile), the prevalence of factor V Leiden was 4.5% and of prothrombin G20210A was 2.5%.⁵⁹ Prevalence rates ranging from 5% to 35% for factor V Leiden, 2.5% to 15% for prothrombin G20210A, and 1% to 23% for protein S deficiency have also been reported. In a systematic review of 3 studies, significant associations were

noted between IUGR and prothrombin G20210A (OR 5.7, 95% CI, 1.2-27) and protein S deficiency (OR 10.2, 95% CI, 1.1-91).⁸²

It is difficult to determine the relationship between thrombophilias and abruptio placentae. This is due to the presence of confounding variables, such as chronic hypertension,^{96,97} and because it is often observed in the setting of other APOs, such as preeclampsia, IUGR, and fetal death. For example, 29% of patients with abruption had a protein S deficiency compared with 0.2-2% in the general population.⁹⁷ Systematic reviews do suggest an association between factor V Leiden and abruptio placentae, but this is based on few studies with confounding factors and low numbers of patients.^{82,83}

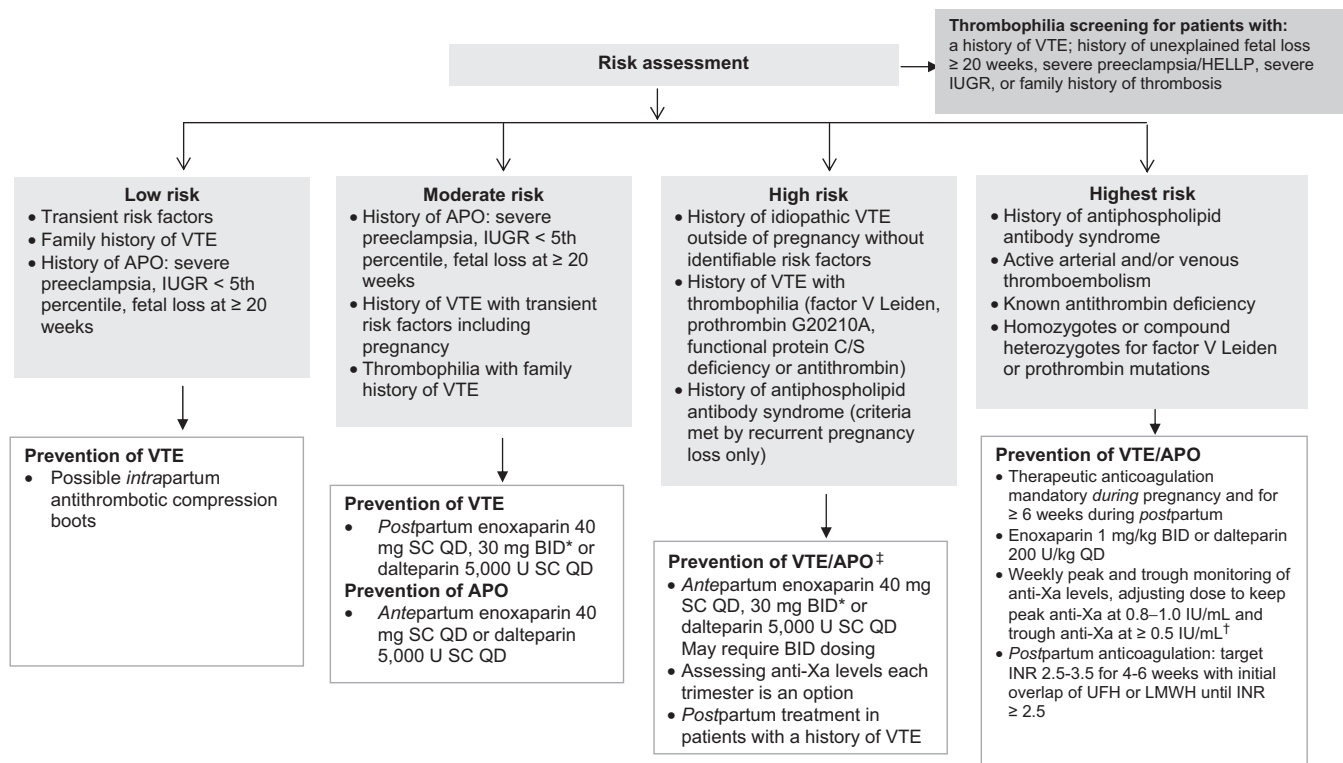
Studies of the possible relationship between thrombophilia and pregnancy loss are plagued by differences in the definitions used for miscarriage and fetal death, the methods used to select patients, and the lack of appropriate, ethnicity-matched controls. Most research suggests that thrombophilias (AT deficiency, protein C or S deficiency, factor V Leiden, prothrombin G20210A, and the most common MTHFR mutation) are not associated with loss of the conceptus or recurrent miscarriage before 10 weeks' gestation (preembryonic or embryonic losses).^{98,99} At the same time, other investigators have reported that untreated women with recurrent miscarriage and factor V Leiden have particularly poor subsequent pregnancy outcomes.^{100,101}

There is more evidence suggesting that loss of the conceptus in the fetal period (loss of the fetus documented to have been alive at or beyond 10 weeks' gestation) is associated with thrombophilias,^{100,102-104} though negative studies also exist.¹⁰⁵ Most case-control and cohort studies suggest a 2- to 4-fold increase in the rate of thrombophilias among women with a history of fetal death, especially in those with more than 1 episode.^{100,102,106-108} In contrast, many studies of the general obstetric population have found a weaker association between thrombophilia and recurrent pregnancy loss.¹⁰⁹⁻¹¹¹ Uteroplacental thrombosis is a common feature in pregnancies with unexplained late fetal loss¹⁰² and could theoretically be reduced by heparin thromboprophylaxis, which may help to prevent a recurrence by decreasing vascular injury and thrombin generation and further reducing thrombosis in the uteroplacental circulation.

Protein Z levels at the 20th percentile (1.30 μ g/mL) are also associated with an increased risk of APO (OR 4.25, 95% CI 1.54-11.76, sensitivity 93%, specificity 32%).¹¹² In the same group of patients, protein S levels were significantly lower in the second and third trimesters in patients with APO compared with patients with normal pregnancy outcome ($34.4 \pm 11.8\%$ vs $38.9 \pm 10.3\%$ and $27.5 \pm 8.4\%$ vs $31.2 \pm 7.4\%$, respectively, for the second and third trimesters; $P < .05$ for both), suggesting that decreased protein S and Z levels are additional risk factors for APO. To further clarify the prothrombotic elements involved, Laude et al¹¹³ studied women with a history of recurrent preg-

FIGURE

Figure risk assessment and prevention of VTE and APOs in pregnant patients

**Monitoring guidelines for patients treated with LMWH or UFH**

1. Anti-factor Xa assay: target peak range (3–4 hours after dosing) is 0.2–0.4 IU/mL for prophylaxis and 0.5–1.0 for treatment (upper range for treatment 0.8–1.0 IU/mL). Target trough range (12 hours after dosing) 0.1–0.3 IU/mL for prophylaxis and 0.2–0.4 IU/mL (> 0.5 IU/mL if highest risk) for treatment.
2. Heparin-induced thrombocytopenia: check platelet counts at start of treatment with heparin, then weekly for 3 weeks.
3. During in-hospital treatment for VTE, fetal surveillance is recommended.

Treatment recommendations based on empiric evidence from the consensus panel

*The choice of enoxaparin dose should be tailored according to the individual patient as these doses have not been compared in this setting.

[†]The dose of enoxaparin may be increased to maintain peak level at the top end of the desired range.

[‡]Aspirin and heparin are recommended in patients with antiphospholipid antibodies.

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nancy loss or late fetal demise (> 10 th week) and their levels of circulating procoagulant thrombin-generating microparticles. Of the patients, 59% in the early pregnancy-loss group (< 10 weeks) and 48% in the late fetal-demise group had increased levels of microparticles. The women were not pregnant at the time of the assessment and these findings would indicate an ongoing preexisting prothrombotic state that may be further enhanced during pregnancy.

SCREENING FOR THROMBOPHILIA

Patients with a history of thrombosis, whether it is of idiopathic origin or associated with pregnancy, with oral contracep-

tive use, trauma, obesity, cancer, or underlying medical conditions, may benefit from being screened for thrombophilia (Figure). Screening patients with a first VTE for thrombophilias is currently the subject of considerable study and debate. Though encouraged by some clinicians, routine testing for thrombophilias may be of limited clinical value. In contrast, patients presenting with recurrent thrombosis or with thrombosis in the setting of a strong family history of VTE may be candidates for thrombophilia testing.

Some obstetricians have recommended thrombophilia screening in women with unexplained fetal loss at 20 weeks' gestation or longer, severe preeclampsia or HELLP, severe IUGR (< 5 th percentile),

or a family history of thrombosis. Evidence in favor of this practice is limited but accumulating at present. The prospective randomized trial by Gris et al¹¹⁴ firmly suggests a potential treatment benefit in screening women with otherwise unexplained fetal death for factor V Leiden, prothrombin G20210A, and functional protein S deficiency.

The basic tests for thrombophilia screening include functional protein C, functional protein S, antithrombin III (AT-III) (functional assay), APC resistance (or factor V Leiden [polymerase chain reaction]), and prothrombin G20210A [polymerase chain reaction]. Other screening for acquired thrombophilic conditions can include testing for

TABLE 5
Heparin administration to prevent APO

Author	N	Drug	Patients studied	Outcome
Riyazi et al ¹³³	26	Nadroparin + ASA 80 mg	Thrombophilia plus prior preeclampsia or IUGR	Treatment associated with lower rates of preeclampsia/IUGR compared with historical control
Brenner et al ¹³⁴	50	Enoxaparin	Thrombophilia plus recurrent fetal loss	Treatment associated with higher live birth rate compared with historical control (75% vs 20%)
Ogueh et al ¹³⁵	24	UFH	Thrombophilia plus IUGR or abruption	No improvement compared with historical control.
Kupferminc et al ¹³⁶	33	Enoxaparin + ASA 100 mg	Thrombophilia plus preeclampsia or IUGR	Higher birth weight and gestational age at delivery compared with previous untreated complicated pregnancies.
Grandone et al ¹³⁷	25	UFH or enoxaparin	Thrombophilia plus APO/	Treatment was associated with lower rates of APO in treated (10%) vs nontreated (93%) patients.
Brenner ¹³⁸	183	Enoxaparin	Thrombophilia plus recurrent fetal loss	Treatment was associated with increased rate of live birth, and decreased rate of preeclampsia and abruption compared with historical control.
Paidas et al ¹³⁹	41	Enoxaparin, dalteparin, or UFH	Thrombophilia plus APO	~80% risk reduction in APO compared with untreated pregnancies.
Gris et al ¹¹⁴	160	Enoxaparin or aspirin	Thrombophilia plus unexplained fetal loss	Enoxaparin was associated with higher live birth rates (86%) compared with aspirin (29%).

anticardiolipin antibodies immunoglobulin G (IgG) and IgM, and lupus anticoagulant. However, not all of these antibodies need to be drawn. A platelet count can be used to screen for thrombocytosis and related disorders. Further supplemental screening may consist of homocysteine, other factor V mutations, thrombomodulin gene variants, protein Z levels, PAI-1 activity levels, PAI-1 4G/5G polymorphisms, MTHFR, homocysteine PAI-1 polymorphisms, and factor evaluation (VII, VIII, IX, XI).

Currently, the costs of routine thrombophilia screening for all patients are prohibitive. Clearly, more evidence-based data from prospective randomized trials evaluating the use of anticoagulation for the prevention of APOs are needed before these costs can be justified.

CONSENSUS PANEL RECOMMENDATIONS FOR THROMBOPHILIA SCREENING

- Patients with a history of thrombosis, unexplained fetal loss at 20 weeks' gesta-

tion or longer, severe preeclampsia/HELLP at less than 34 weeks' gestation, severe IUGR, or a family history of thrombosis may benefit from thrombophilia screening.¹¹⁴ The basic screening tests include factor V Leiden mutation, prothrombin G20210A mutation, functional protein C and S deficiencies, AT-III deficiency, lupus anticoagulant, homocysteine level, and anticardiolipin antibodies.⁷⁹ (Level IIIc)

RISK ASSESSMENT AND ANTITHROMBOTIC RECOMMENDATIONS DURING PREGNANCY

Patients can be classified according to their risk for VTE, their risk of an APO, or both. Antithrombotic recommendations are based on an assessment of an individual patient's level of risk, and are outlined in the Figure. It should be emphasized that the risk categories and treatment regimens are based on level II and III studies and/or extrapolated from level I nonpregnant studies.

Typically, patients at highest risk are on coumarin before pregnancy and ideally should be converted to LMWH before conception or as soon as the patient presents for care. Previous guidelines have recommended that target peak anti-Xa levels (measured 4 hours after a subcutaneous dose) should be 1.0-1.2 IU/mL.⁵ Therapeutic anticoagulation should be considered in high-risk women during pregnancy but using prophylactic dosing and less frequent monitoring than in the highest-risk group. The prophylactic and therapeutic doses for the most commonly used LMWHs are illustrated in Table 5.²⁴ Because of the altered pharmacokinetics of heparin metabolism in pregnancy,^{18,115-117} dosage adjustment may be necessary to achieve desired adequate peak or trough anti-Xa levels and thus monitoring for therapeutic anticoagulation is suggested. Dosing adjustment is also needed to achieve adequate levels in obese patients. If UFH is used for therapeutic anticoagulation, higher doses and 3 times daily dosing are usually required to maintain adequate

TABLE 6
Prophylactic and therapeutic doses for the most commonly used LMWHs

LMWH	Proprietary name, manufacturer	Anti-factor-Xa/IIa activity	Prophylactic dosage for VTE	Therapeutic dosage for VTE
Enoxaparin sodium	Lovenox, Sanofi-Aventis	2.7/1	40 mg (4000 IU) QD	1 mg (100 IU)/kg BID
Dalteparin sodium	Fragmin, Pfizer Corporation	2.1/1	2500-5000 IU QD or 2500 IU BID	100 IU/kg BID
Nadroparin calcium	Fraxiparin, GlaxoSmithKline	3.2/1	3075 IU QD	170 IU/kg QD or BID
Tinzaparin sodium	Innohep, LEO Pharma	1.9/1	2500-4500 IU QD	175 IU/kg QD
Ardeparin sodium	Normiflo, Wyeth-Ayerst	2.0/1	100 IU/kg per day BID	NA
Reviparin sodium	Clivarin, Knoll AG	3.5/1	1432-3436 IU antifactor Xa QD	142 IU/kg BID

NA, data not available.

Adapted from Laurent et al²⁴ with permission from Wolters Kluwer Health.

anticoagulation peak levels to rise the activated partial thromboplastin time (aPTT) to 2-2.5 times normal.¹¹⁸

Women at moderate risk may be offered prophylactic doses of LMWH (Figure), with 2500-5000 IU dalteparin twice daily (BID), 40 mg enoxaparin once daily (QD), or 30 mg enoxaparin BID. Although the relative efficacy of these 2 enoxaparin doses has not been studied, and the use of 40 mg enoxaparin QD is common practice, members of the consensus panel have divided opinions for the choice of dose, based on the pharmacokinetic properties of LMWH in pregnancy.⁷ Until studies comparing the 2 regimens are published, clinicians should choose the most appropriate regimen for their patient and her clinical situation. Some investigators aim to achieve peak anti-Xa levels (3-4 hours after dosing) ranging from 0.2-0.4 IU/mL but, in general, monitoring is not necessary for these patients. Women at low risk may not need antepartum prophylaxis, but some authors recommend postpartum prophylaxis ranging from 3 days to 6 weeks, particularly in obese women and women with cesarean birth.^{24,43}

MONITORING OF PATIENTS ON LMWH OR FACTOR-XA INHIBITORS

Where monitoring is indicated, an anti-Xa assay must be used because the aPTT is insensitive to LMWHs and Xa inhibitors.^{26,29} Most commonly, anti-Xa-activity assays involve setting up a standard curve using the drug in question and measuring drug activity using a chromogenic substrate, but this test is not routinely

available in clinical laboratories. Most laboratories that offer this test have it set up for 1 of the LMWHs (eg, enoxaparin, which has a recommended therapeutic range of 0.5-1.0 anti-Xa units/mL and a prophylactic range of 0.2-0.4 IU/mL). As the various LMWHs have different factor Xa/IIa activity (Table 5),²⁴ the test *must* be calibrated for the drug in question. For example, a factor Xa assay set up for enoxaparin should not be used interchangeably for another LMWH or anti-Xa drug, as it may give erroneous readings.

PREVENTION AND COUNSELING FOR VTE

Current recommendations for thromboprophylaxis during pregnancy are based largely on case series and extrapolation from studies of nonpregnant patients. Because of the incidence of recurrent VTE being low, studies need to be extremely large to obtain sufficient power to demonstrate the efficacy of any strategy and thus far, such a randomized prospective trial in pregnancy has not been done. In the nonobstetric literature, thromboprophylaxis is prescribed to protect patients during short periods covering specific vulnerable events such as orthopedic surgery. In pregnancy, thromboprophylaxis is given for prolonged periods because pregnancy and the puerperium is a hypercoagulable state lasting approximately 308 days from conception until 6 weeks after delivery. Maintaining a constant level of anticoagulation, with changing renal clearance, increasing weight, and superimposed periods of even higher risk,

such as cesarean delivery, bed rest, or the postpartum period, creates a very different approach to thromboprophylaxis compared with the nonpregnant state. Dosages and monitoring guidelines for nonpregnant women cannot be extrapolated accurately to pregnant women. All protocols and regimens of thromboprophylaxis in pregnancy entail extensive patient and clinician interaction. Modifications during pregnancy are common, and treatment plans need to be individualized with informed consent between patients and their physicians.

HOW TO MANAGE PATIENTS WITHOUT PRIOR VTE OR THROMBOPHILIA

Thromboprophylaxis in pregnancy is accomplished primarily with self-administered subcutaneous UFH or LMWH. However, because thromboprophylaxis carries a risk of bleeding, HIT, and osteoporosis when given for prolonged periods, its use may only be justified or cost effective in selected pregnant women. Nevertheless, pregnant women with 1 high-risk factor or multiple (> 3) moderate-risk factors for VTE (Table 3)^{37,77,78} are considered for thromboprophylaxis in the United Kingdom¹¹⁹ (Table 6),¹¹⁹ although more data are required before this approach can be accepted in the United States. The Confidential Enquiries into Maternal Deaths in the United Kingdom revealed that, when maternal death occurred due to VTE, 1 or more of these risk factors was present in 80% of the women.¹²⁰

1. Thromboprophylaxis during cesarean delivery. Thromboprophylaxis during cesarean delivery is not widely used in the United States. Expert panels^{8,75} have published recommendations for thromboprophylaxis in pregnancy but they do not specifically address cesarean delivery. In 1995, the Royal College of Obstetricians and Gynaecologists (RCOG) published recommendations for thromboprophylaxis during cesarean delivery (Table 6),¹¹⁹ but only one fifth of physicians in the United Kingdom were found to be following them. As a consequence, the RCOG now recommends that all women undergoing cesarean delivery should receive heparin thromboprophylaxis.¹²⁰

Currently, only 4 prospective randomized trials of thromboprophylaxis during cesarean delivery have been published, and none are of adequate size to determine whether thromboprophylaxis for routine cesarean delivery is warranted.¹²¹ Similarly, the effectiveness of nonpharmacologic mechanisms of thromboprophylaxis, such as venous compression stockings and pneumatic compression boots, have not been studied in pregnant patients. Although there are compelling data from both meta-analyses and several placebo-controlled, double-blind randomized trials demonstrating that there is no significant increase in major bleeding from thromboprophylactic regimens of UFH or LMWHs, there is a significant increase in minor bleeding (66%) and impaired surgical hemostasis observed with these drugs.¹²² Not only is there a lack of data regarding the efficacy of thromboprophylaxis in pregnancy and the potential for increased morbidity, but concern about increased costs associated with thromboprophylaxis during cesarean delivery also contributes to the lack of prophylaxis. Until a prospective randomized trial of adequate sample size is conducted that addresses this question, routine pharmacologic thromboprophylaxis during cesarean delivery with UFH or LMWH cannot be recommended. However, such a trial is unlikely given the low VTE incidence rates and cost concerns. Because intermittent pneumatic compression may be as effective as UFH or LMWH, and does not introduce risk to the patient,¹²³ in the opin-

ion of the Working Group mechanical thromboprophylaxis may be considered and perhaps recommended in patients with multiple risk factors.

CONSENSUS PANEL RECOMMENDATIONS FOR MANAGING PATIENTS WITHOUT PRIOR VTE OR THROMBOPHILIA

- Thromboprophylaxis use in all pregnant patients without prior VTE or thrombophilia may only be justified or cost effective in selected pregnant patients.¹²¹ (Level IIIC)
- There are insufficient data to recommend routine pharmacologic prophylaxis in patients undergoing cesarean delivery.¹²¹ (Level II-2B)
- Intermittent pneumatic compression may be considered in patients undergoing cesarean delivery with multiple VTE risk factors.¹²³ (Level IIIC)

HOW TO MANAGE PATIENTS WITH A HISTORY OF VTE

1. Provoked VTE or temporary risk factors. It is unclear whether women with a history of provoked VTE or temporary risk factors, such as a bone fracture or a prolonged period of immobility, are at increased risk of VTE during pregnancy. They may be at lower risk than women with a history of idiopathic VTE but at higher risk than patients with no history of any VTE.⁵² However, as a consequence of this theoretical increased risk over the general obstetric population, it is reasonable to counsel the patient accordingly. At present, the need for either antepartum or postpartum thromboprophylaxis is unsettled, and clinicians are forced to manage cases on an individual basis.

2. Idiopathic VTE. Few data are available on the management of pregnant women who have a history of idiopathic VTE prior to the current pregnancy. These patients are likely to be at higher risk of VTE compared with individuals without a history.⁴⁶ One of the difficulties faced by physicians in counseling such patients lies in weighing the risks of treatment with the risk of developing a thrombus. Prophylactic anticoagulation

with UFH or LMWH administered antenatally and during the 6 weeks postpartum may be an appropriate option for some patients. Patients should also be encouraged to regain mobility after childbirth, but in individuals in whom this is not possible, compression stockings could be worn.

3. How to manage patients with a history of 2 or more VTEs. Few data are available to suggest that, if a person has had 2 or more episodes of idiopathic VTE, she will be at increased risk of VTE during pregnancy. Theoretically, this group of patients may have an even higher risk of VTE compared with patients with no history and so may already receive lifelong anticoagulation. If not, then antenatal and postpartum prophylactic anticoagulation with UFH or LMWH^{124,125} and patient counseling should be mandatory in these patients. However, the patient must be informed of the limited amount of data available to support the use of anticoagulants in this setting.

4. How to manage patients with prior VTE and thrombophilia. Most experts agree that the management of pregnant women with prior VTE and an acquired or inherited thrombophilia requires some sort of thromboprophylaxis in the antepartum and postpartum periods.^{43,126-128} Although not prospectively evaluated in a clinical trial, the intensity of thromboprophylaxis should reflect the relative risk conferred by having that thrombophilia. Most authors recommend full anticoagulation using aspirin and heparin in women with a prior VTE and antiphospholipid syndrome. In women with low-risk thrombophilias, such as hyperhomocysteinemia or factor V Leiden/prothrombin G20210A heterozygosity, prophylactic doses of UFH or LMWH are probably sufficient. In pregnant women with high-risk thrombophilias, such as AT-III deficiency, homozygotes for either factor V Leiden or the G20210A mutation, or compound heterozygotes for factor V Leiden and prothrombin G20210A mutations, adjusted-dose UFH or LMWH to achieve a target aPTT (2-2.5 control) or anti-Xa level (0.5-1.0) should be recommended. These relative risks and the recom-

mended intensity of prophylaxis are summarized in Table 7.^{56,129,130}

CONSENSUS PANEL RECOMMENDATIONS FOR MANAGING PATIENTS WITH PRIOR VTE

- In patients with a history of idiopathic VTE, prophylaxis with LMWH or UFH may be considered antepartum and for 6 weeks postpartum.⁴⁶ (Level IIC)
- In patients with a history of 2 or more VTE episodes, antenatal and postpartum prophylaxis with LMWH and UFH should be used.^{124,125} (Level IIC)
- Patients with a history of VTE and thrombophilia should receive prophylaxis with LMWH or UFH. Prophylaxis intensity should be tailored to the risk conferred by the thrombophilia (Table 7^{56,129,130}).^{43,126-128} (Level II-3C)
- Patients with a history of VTE on pregestational full anticoagulation should be maintained on full anticoagulation during pregnancy. (Level IIC)

HOW TO MANAGE PATIENTS WITH NO PRIOR VTE OR ADVERSE PREGNANCY OUTCOMES BUT WITH THROMBOPHILIA

Retrospective data have been used to suggest that previously asymptomatic women with an inherited thrombophilia are at increased risk of VTE and a potentially poor obstetric outcome.¹³¹ However, the only prospective study involving previously asymptomatic women who tested positive for factor V Leiden revealed no higher rates of VTE, preeclampsia, or fetal death in comparison with those women who tested negative for this mutation.¹³² Also, it is likely that the level of risk varies according to the type of thrombophilia and the presence or absence of other risk factors, such as immobilization, obesity, or smoking. To avoid overtreatment, risk-assessment categories (Figure) are used to identify patients who warrant either prophylactic or therapeutic treatment with anticoagulants. Regardless of their antecedent

TABLE 7
Relative risk of recurrent VTE in pregnancy^{56,129,130}

Disorder	Risk of VTE	Prophylaxis intensity
Factor V Leiden heterozygote	3- to 9-fold	Low-dose prophylaxis
Factor V Leiden homozygote	49- to 80-fold	Adjusted-dose therapy
Prothrombin G20210A heterozygote	2- to 9-fold	Low-dose prophylaxis
Prothrombin G20210A homozygote	16-fold	Adjusted-dose therapy
Antithrombin III deficiency	25- to 50-fold	Adjusted-dose therapy
Protein C deficiency	3- to 15-fold	Low-dose prophylaxis
Protein S deficiency	2-fold	Low-dose prophylaxis
Hyperhomocysteinemia	2.5- to 4-fold	Low-dose prophylaxis
Antiphospholipid antibodies	5.3-fold	Adjusted-dose therapy
Compound heterozygote of Factor V Leiden and Prothrombin G20210A	150-fold	Adjusted-dose therapy

history, asymptomatic pregnant patients with AT-III deficiency or those who are homozygotes or compound heterozygotes for the factor V Leiden or prothrombin G20210A mutations are at very high risk for maternal thromboembolic disorders and require UFH or LMWH throughout pregnancy.⁴³ With the exception of the above, there does not appear to be any justification for antenatal treatment with UFH or LMWH in asymptomatic patients incidentally found to have an inherited thrombophilia and no history of prior VTE or characteristic adverse pregnancy outcomes.^{7,43,124} Short-term thromboprophylaxis with UFH or LMWH might be considered in pregnant women with thrombophilia and no history of VTE or adverse pregnancy outcomes when other risk factors are also present, such as multiple family members with VTE or medical complications known to be associated with VTE.

Current guidelines are based on recommendations by the American College of Chest Physicians (ACCP) and are grade 1C (equivalent to level II-2 in these guidelines), derived mainly from observational studies that are likely to be revised in the future as well-controlled obstetric studies become available.⁷ Table 7^{56,129,130} and the Figure illustrate risk categories for patients with a thrombophilia and the recommended treatments and dosages.^{56,129,130}

CONSENSUS PANEL RECOMMENDATIONS FOR MANAGING PATIENTS WITH NO PRIOR VTE OR APO BUT WITH THROMBOPHILIA

- There is insufficient evidence to recommend anticoagulant drug treatment during pregnancy in asymptomatic women with no prior VTE or APO. Some such patients will have additional risk factors that may lead the clinician to treat.¹³² (Level IIC)
- Asymptomatic women with AT deficiency or who are homozygotes or compound heterozygotes for the factor V Leiden and prothrombin G20210A mutations require therapeutic UFH or LMWH throughout pregnancy.⁴³ Asymptomatic patients incidentally found to have other inherited thrombophilia and no prior VTE or APO do not require UFH or LMWH.^{5,43,124} (Level II-2B)
- For patients being treated with LMWH, if an antifactor-Xa level is evaluated, the target peak range (drawn 3-4 hours after subcutaneous administration) is 0.2-0.4 IU/mL in prophylactic settings and 0.5-1.0 IU/mL in the therapeutic setting. Trough levels (12 hours after dosing) should be between 0.1-0.3 IU/mL in a prophylactic setting and 0.2-0.4 IU/mL in a therapeutic setting.^{24,124,124,130} (Level II-2B)

- Platelet counts should be drawn for all patients using heparin therapy.¹³⁰ (Level IIIC)
- One possible regimen is drawing before initiation of heparin therapy and every week for 3 weeks.¹³⁰
- Fitted compression stockings, calcium, and vitamin D supplementation may be of benefit.⁴³ (Level IIIC)

HOW TO MANAGE PREGNANT WOMEN WITHOUT THROMBOPHILIA OR VTE BUT WITH OTHER RISK FACTORS

Pregnant women who have received ovulation-induction drugs to achieve pregnancy have supraphysiologic levels of estrogen throughout the first and early second trimester and are possibly at higher risk of VTE. Other factors associated with VTE include ovarian hyperstimulation syndrome, hyperemesis gravidarum, dehydration, prolonged bed rest, nephrotic syndrome, and surgery. Temporary use of intermittent compression devices, and/or UFH or LMWH prophylaxis might be considered, especially in the presence of obesity, surgery, or prolonged bed rest. Later in pregnancy, women placed on prolonged bed rest for premature labor, especially if obese, may be at heightened risk for VTE, and prophylactic measures should be considered. There are currently no data on the use of prophylactic heparin in this population.

HOW TO MANAGE PATIENTS WITH A POOR OBSTETRIC HISTORY

Counseling for women with a poor obstetric history is based on the type of thrombophilia identified.

Ultimately, the risks and benefits of treatment should be discussed with the patient so that she can make an informed decision. Patients with a history of thrombophilia, whether inherited or acquired, should be counseled regarding the inherent risks associated with estrogen therapy (ie, with oral contraceptives or hormone replacement therapy and selective estrogen receptor modulator-class medications). Women with mild hyperhomocysteinemia may use estrogen-based med-

ications, as estrogen decreases levels of homocysteine.

There are limited data available investigating the use of anticoagulation in women with a history of APOs, with the existing studies comprising small numbers of patients, various indications and dosages of heparin therapy, and including other medications (Table 8^{114,133-139}). Hence, we are currently unable to draw adequate conclusions about the efficacy and safety of LMWH in these patients, although most authorities will offer LMWH therapy to women with thrombophilia and multiple pregnancy losses. In 2003, a Cochrane review found that there were no completed trials to determine the effects of heparin on pregnancy outcomes for women with thrombophilia.¹⁴⁰ In a more recent Cochrane review evaluating the use of anticoagulation for the treatment of recurrent pregnancy loss (> 2 spontaneous losses or 1 intrauterine fetal demise) in women without antiphospholipid syndrome but including inherited thrombophilias, only 2 randomized studies were identified, and they concluded that the evidence for using aspirin or heparin in this setting is too limited to make recommendations.¹⁴¹

PRACTICAL MANAGEMENT OF ANTICOAGULATION AND PREGNANCY: HIT AND HEPARIN ALLERGY

HIT may affect up to 3% of patients exposed to heparin.²³ Type I thrombocytopenia occurs within a few days of heparin exposure, is self-limited, and benign. Type II is an autoimmune, immunoglobulin-mediated syndrome associated with venous and arterial thrombosis and may occur from 5 days to 3 weeks after starting treatment. Because type I is initially difficult to differentiate from type II, any drop in platelet count below 150,000, or drop of 50% from baseline, should signal the clinician to stop heparin therapy. Importantly, this includes heparin flushes of iv lines. Fortunately, HIT is extremely rare in pregnancy¹⁴² and very rare in patients treated with LMWH. In fact, in more than 1100 pa-

tients, only 1 case of HIT was reported.^{27,143}

Paradoxically, more than half of the patients with asymptomatic HIT experience a thrombotic event in the following 30 days.¹⁴² Patients should therefore be treated with an alternative anticoagulant such as the synthetic pentasaccharide fondaparinux, which selectively inhibits Factor Xa. If the patient has no evidence of active thrombosis, prophylactic fondaparinux sodium (2.5 mg QD) is recommended, whereas those with an active thrombosis should be given therapeutic levels of the drug (5 mg for body weight < 50 kg, 7.5 mg for body weight 50-100 kg or 10 mg for body weight > 100 kg).³⁰ Fondaparinux does not cross the placenta and is considered a class B medication but is not FDA approved for use in pregnancy.^{30,144} Postpartum, fondaparinux should be used for the first several days until warfarin therapy has raised the INR to 1.5-2.0.

Some women can develop a severe allergic reaction to heparin, which can initially present with large red plaques but can progress to areas of massive skin necrosis. In gravid women with a severe heparin allergy, heparin should be discontinued and alternative therapy begun, in a similar manner to women who have HIT develop.^{145,146} Alternatively, many experts believe a mild local allergy can be managed without immediate discontinuation.

In these cases, consulting a hematologist is essential for the patients' overall care.

CONSENSUS PANEL RECOMMENDATIONS FOR THE EVALUATION OF HIT

- Platelet counts should be checked at the start of treatment with UFH, then weekly for the next 3 weeks.¹³⁰ (Level II-3A)
- Any patient who shows a decrease in platelets (< 100,000) should have treatment discontinued.⁷ (Level II-3A)
- Consulting a hematologist is essential for the patients' overall care. (Level IIIC)

PRACTICAL MANAGEMENT OF ANTICOAGULATION AND PREGNANCY: THROMBOLYTICS

There are no conclusive data to direct the use of either thrombolysis or surgical embolectomy for the treatment of massive thromboembolism in pregnant and nonpregnant patients. Anecdotal experience and several published cases suggest that the use of thrombolytic drugs during pregnancy may be safe and effective and might be considered when at risk of maternal death or chronic venous insufficiency, especially in the first or early second trimester of pregnancy. Dissolution of massive and/or life-threatening thromboembolism during pregnancy has been reported.¹⁴⁷⁻¹⁶² The use of thrombolytic drugs during pregnancy is investigational with very limited safety data. The reports demonstrate the potential for nearly immediate resolution of massive blood clots using either placement of a catheter within the clot allowing a local pulsed spray of a thrombolytic drug or with systemic therapy. Catheter-directed thrombolysis is a promising investigational technique that could be considered during pregnancy in severe cases when the acute or chronic risk of thromboembolism outweighs the potential risk of pregnancy loss.

TREATMENT OF VTE IN PREGNANCY

The management of therapeutic anticoagulation during pregnancy must be undertaken with extraordinary care and an in-depth understanding of maternal and fetal physiology and the effects of the therapy on both mother and fetus. Therapeutic considerations in pregnant women are quite different from nonpregnant patients. More importantly, knowledge of the effects of treatment on the fetus before, during, and after birth is critical. It is also important that care providers are intimately familiar with common obstetric problems, including premature labor or rupture of membranes, diabetes, and preeclampsia. It is not intuitive to nonobstetric care providers that time of birth is often unpredictable. Even if an elective induction or cesarean

birth is planned, obstetric problems may unexpectedly necessitate early delivery.

DIAGNOSIS OF VTE

The suspicion of VTE based on clinical history and physical examination should be established by diagnostic studies including at least 1 of the following: Doppler ultrasound, venography, lung ventilation/perfusion scanning, spiral computed tomography, pulmonary venography, and magnetic resonance angiography. A highly confident diagnosis of VTE during pregnancy should be established because both diagnosis and treatment have significant immediate and remote ramifications; empiric therapy with a questionable diagnosis is highly discouraged. Patients with a confirmed diagnosis of VTE are usually hospitalized for initiation of treatment. If there is any evidence of, or significant risk for, cardiopulmonary compromise, admission to a critical care unit should be considered. Fetal surveillance, including ultrasound and/or fetal heart rate monitoring, if appropriate, should be obtained daily.

MANAGEMENT OF VTE

Before implementing anticoagulation therapy, a thrombophilia panel should be obtained including factor V Leiden mutation, prothrombin G20210A mutation, protein C and S deficiencies, AT-III deficiency, lupus anticoagulant, homocysteine level, and anticardiolipin antibodies. LMWH therapy may be initiated immediately or after 5-10 days of treatment with UFH. The largest volume of clinical experience with LMWH in pregnancy is with enoxaparin and dalteparin.^{24,125,143,163-165} At least 1 small randomized, controlled trial (level I data) in pregnancy concluded that treatment with LMWH was safe and effective, and was associated with fewer bleeding complications than UFH.¹⁶⁵

Minimum starting therapeutic doses of LMWH in pregnancy should be: enoxaparin 1 mg/kg sc BID or dalteparin 100 IU/kg sc BID. As the patient is hospitalized with a documented VTE, slightly higher starting doses may be initiated because of the enhanced renal

clearance and plasma volume during pregnancy. Some panel members believe that in pregnant women with a large VTE, a starting dose of 1.2 mg/kg enoxaparin BID is necessary to achieve therapeutic anti-Xa levels. The choice of enoxaparin regimen should therefore be tailored to each patient's clinical situation. There is considerable evidence that pregnancy may require higher doses to achieve similar anti-Xa levels compared with nonpregnant women.^{115,117} If readily available, initial therapy should include a peak anti-Xa level that is drawn 3-4 hours postinjection after the third dose.^{117,166,167} Trough levels approximately 1 hour or less before the subsequent dose should be kept at or above 0.4 IU/mL.

The use of temporary venocaval filters should be considered in pregnant patients when the thrombus is extensive (extending into the upper femoral, iliac, or vena caval system) or the patient is at particularly high risk for PE, such as those who have failed previous treatment or women with a history of PE. Graduated compression stockings can be used, and patients should be encouraged to ambulate as soon as possible after starting treatment. Acute therapy should continue in the hospital for 3-7 days depending on the extent of VTE and the patient's clinical status. Calcium and vitamin D supplementation should be started and continued for the duration of treatment with LMWH or UFH. Patients may also need a stool softener to avoid constipation. Patients should be instructed on self-injection and home use of LMWH. Subcutaneous injection ports are available for patients who have a significant fear of self-injection, although it is not known how or if they affect the absorption of LMWH. These ports should be changed weekly.

MONITORING PATIENTS

With the initial hospital therapy, peak anti-Xa levels should be kept well within the therapeutic range for the hospital's laboratory. The lower therapeutic range for anti-Xa level is 0.5-0.6 IU/mL and the upper limit is 0.8-1.0 IU/mL (Figure). For particularly high-risk patients or for

those with a large and significant thrombosis and/or embolus in pregnancy, trough levels (drawn 12 hours after the dose) might be considered in the initial treatment to achieve 24 hours of continuous therapeutic anti-Xa levels (usually > 0.5 IU/mL for highest-risk patients, depending on the laboratory). Reaching a therapeutic trough level may require increasing the dose so that peak anti-Xa levels exceed the upper therapeutic limit, or increasing the frequency of administration to 3 times daily. Peak anti-Xa levels in the range of 1.0-2.0 IU/mL have been reported without bleeding complications in nonpregnant patients,¹⁶⁸ and anecdotal experience suggests that they are well tolerated in pregnancy. Monitoring of anti-Xa levels in pregnant women with acute VTE would be especially important in patients with impaired renal or hepatic function, extremes of weight (< 50 kg or > 100 kg) or in the presence of other risk factors for bleeding, such as thrombocytopenia, recent surgery, or severe preeclampsia.

Monitoring for HIT should be carried out in all patients after starting treatment with UFH or LMWH (Figure). Fecal occult-blood tests should be performed periodically for patients on therapeutic doses of these drugs. After discharge from hospital, therapeutic LMWH should be continued throughout pregnancy and the postpartum.^{7,24}

CONSENSUS PANEL RECOMMENDATIONS FOR TREATMENT OF VTE

- Treatment should be initiated immediately on diagnosis of VTE with either LMWH or UFH for 5-10 days, followed by LMWH.^{7,12-28,30-33} (Level II-1A)
- LMWH may be preferable to UFH in these patients.¹⁸⁻²⁴ (Level IB)

ANTICOAGULATION IN PATIENTS DURING LABOR AND DELIVERY, AND THE POSTPARTUM

Patients receiving full anticoagulation with UFH, LMWH, or warfarin should be counseled about the risks and benefits of anticoagulation, both maternal and fetal, and understand that their preg-

nancy will be managed by a “team” approach. This team includes the obstetrician, hematologist, pulmonologist, anesthesiologist, and cardiologist as required. The patient should also be counseled that vaginal delivery is preferable to cesarean delivery, with cesarean delivery reserved for the usual maternal and fetal indications. Patients on full anticoagulation with warfarin are generally transitioned to either LMWH or UFH at 32-36 weeks’ gestation at full anticoagulation.⁷ Before delivery or induction, it has been recommended that IV UFH, due to a shorter half-life, be implemented to achieve an aPTT level 1.5-2.0 times the patient’s baseline or to attain a heparin level of 3-7 U/mL.^{7,169} Treatment with UFH is stopped during labor^{169,170} and is discontinued 3-6 hours before elective cesarean delivery.¹⁷⁰ Both of these approaches enable the patient to have anesthetic and delivery options. The American Society of Anesthesiologists (ASA) allows for the use of regional analgesia/anesthesia 12 hours after a prophylactic dose and 24 hours after a therapeutic dose of LMWH. There are considerable benefits for continuing prophylactic or therapeutic LMWH up until onset of labor and/or rupture of membranes. If the patient labors before the ASA time limits, then aggressive use of an IV narcotic provides safe and satisfactory analgesia, and general anesthesia may be used for cesarean delivery if necessary. Another alternative is to schedule induction of labor with discontinuation of the LMWH to achieve the ASA guidelines. However, it should be emphasized that induction of labor in a patient with an unfavorable cervix may increase the risk of cesarean delivery, which should be avoided if at all possible because of the risk of VTE or major hemorrhage.¹⁷¹ Full anticoagulation with LMWH can be maintained during the labor and delivery process with the appropriately counseled patient and with the correct clinical indications (ie, recent VTE, mitral stenosis with atrial fibrillation).^{169,172} Data from several small studies have demonstrated no increased risk of major bleeding with surgical procedures, operative vaginal delivery, and cesarean delivery in patients treated with LMWHs.^{27,170-174}

This has also been demonstrated in a recent prospectively studied cohort of patients receiving enoxaparin at prophylactic and full anticoagulation doses.¹⁷⁵

Patients with a recent history of VTE who have been managed with UFH or LMWH at full anticoagulation may be managed during labor as defined above or switched to prophylactic dosing of LMWH during the labor and delivery process.^{7,169} However, the anesthetic options are limited. In a cesarean delivery, endotracheal intubation with central induction of anesthesia is indicated if delivery takes place within 12 hours of taking a prophylactic dose of LMWH. Patients who have had a deep vein thrombosis within the last 3 months and are fully anticoagulated with UFH or LMWH can be switched to prophylactic LMWH or UFH at 36 weeks’ gestation. Treatment with LMWH or UFH can be withheld during labor.^{24,169,172} Patients who receive prophylactic doses of UFH or LMWH can stop treatment 12-24 hours before induction or elective cesarean delivery.^{169,176} Patients receiving full anticoagulation with LMWH should have the LMWH withheld for 24 hours before induction of labor or cesarean delivery.⁷

SPECIAL CONSIDERATIONS

During labor and delivery, including cesarean delivery, pneumatic compression devices for the lower extremities have been recommended. Stronger evidence supporting their use using data from the nonpregnant surgical population has been extrapolated to cesarean deliveries.¹¹⁹

Antithrombin (AT) is normally present in human plasma at 12.5 mg/dL and is the major inhibitor of thrombin, in addition to inhibiting other activated clotting factors such as XII, IX, XI, and X. Patients who are AT-deficient are thought to be highly “hypercoagulable” individuals during the antepartum, intrapartum, and postpartum periods.^{7,130,177-181} These patients should receive AT concentrate in addition to adjusted-dose anticoagulation if they experience an acute arterial or VTE.^{130,180,182,183} Recovery may vary, and in addition to baseline levels, an AT level

should be measured 20-30 minutes after infusion of the first dose of AT-III.¹⁷⁸ It is generally recommended that, after the initial dose of AT-III, AT levels be evaluated every 12 hours after administration and before the next dose of AT-III to maintain levels greater than 80%.^{177,184} After some surgical procedures, hemorrhages, acute arterial, or venous thrombosis, and during IV heparin administration, the half-life of AT-III has been reported to be shortened.¹⁷⁷ During these scenarios the AT levels should be monitored more frequently and replacement be administered as necessary.¹⁷⁷ In obstetric patients in whom an infusion is indicated for hereditary deficiency to control a thrombotic episode or to prevent thrombosis, AT levels should be returned to normal and maintained at this level for 2-8 days.¹⁷⁷ Concurrent administration of an anticoagulant should be based on medical judgment. Involving a hematologist experienced in AT-III deficiency is essential for the patients' overall care.

CONSENSUS PANEL RECOMMENDATIONS FOR MEASURING ANTITHROMBIN LEVELS

- Evaluate AT levels before infusion and 20 minutes after infusion (peak).¹⁷⁷ (Level IIIC)
- Evaluate AT levels after 12 hours and then preceding the next infusion (trough).^{177,184} (Level IIIC)
- Obtain subsequent AT levels before and 20 minutes after each infusion until predictable peak and troughs have been achieved (ranging from 80% to 120%).^{177,184} (Level IIIC)
- Maintain plasma levels between 80% and 120% with the administration of AT-III at doses of 60% of the initial loading dose given every 24 hours. Subsequent doses should be adjusted based on AT levels.^{177,184} (Level IIIC)
- Involving a hematologist experienced in AT-III deficiency is essential for the patients' overall care. (Level IIIC)

The above recommendations for dosing and establishing the maintenance dosage should be interpreted as general guidelines for therapy only. The exact

doses for loading and maintenance, as well as dosing intervals, should be individualized for each patient, their clinical condition, response to therapy, and the AT-III level.¹⁷⁷

POSTPARTUM MANAGEMENT

Patients who require full anticoagulation during the antenatal period will generally require full anticoagulation during the postpartum period. Patients treated previously with warfarin can be given this drug after delivery because it is safe to use while breast feeding.^{7,185} Patients who require warfarin therapy are generally treated with LMWH or IV UFH and are then transitioned to warfarin.^{7,185} It is safe to resume UFH/LMWH therapy within 12 hours of delivery. A period of at least 3-5 days in which the patient is fully anticoagulated with UFH or LMWH and fully anticoagulated with warfarin (INR 2-3) is often needed before treatment with UFH or LMWH can be stopped.¹⁸⁵ At least 2 therapeutic INRs should be confirmed before stopping UFH or LMWH therapy. Failure to perform the transition therapy or over-aggressively increasing the warfarin dose because of a low INR can result in maternal complications, such as bleeding from the involuting placental site, and, starting warfarin therapy without concomitant LMWH or UFH may lead to paradoxical coumadin skin necrosis.¹⁸⁵ The initial dose of warfarin should not exceed 5 mg or the dose taken before pregnancy, whichever is less.¹⁸⁵ Only physicians experienced in anticoagulation should perform the transition therapy.

Patients who receive full anticoagulation with UFH or LMWH during the antenatal period should be weighed before starting treatment in the postpartum because their body weight may have changed significantly and they may require a lower dose of UFH or LMWH. In patients in whom warfarin therapy is appropriate, transitioning can be carried out as described previously. If full anticoagulation is needed because of a recent episode of VTE, treatment with warfarin is often recommended for 3-6 months postpartum.^{7,178,185} Life-long anticoagulation with warfarin is generally re-

quired in AT-deficient patients, patients with a history of arterial thrombosis, patients with 2 or more episodes of VTE, and in women with antiphospholipid syndrome.^{7,185} If full anticoagulation with LMWH is desired (ie, for patients with homozygous prothrombin G20210A), treatment with LMWH is generally continued for 6-8 weeks postpartum and then stopped.^{7,8,169} Warfarin may also be used in this scenario.^{7,169} When LMWH is given once daily, the first peak antifactor-Xa level is obtained 3-4 hours after the third dose.^{7,172,185,186} Peak levels considered to be acceptable for prophylaxis are 0.2-0.4 IU/mL. Peak levels considered acceptable for full anticoagulation are 0.5-1.0 IU/mL.

Patients who receive prophylactic doses of LMWH or UFH for past or recent VTE should continue this dosing regimen for 6-8 weeks postpartum.^{7,169} Patients with thrombophilia without evidence of past or recent VTE who are managed with prophylactic UFH or LMWH can receive the same dose 6-8 weeks postpartum.^{7,24,125,187} However, this approach is controversial and further clinical investigation is necessary as some physicians believe that these patients can be followed expectantly during the postpartum period.^{7,178} Most authors agree that patients without a history of VTE but with thrombophilia, or with recurrent pregnancy loss with thrombophilia, who undergo a cesarean delivery should receive postoperative/postpartum treatment with prophylactic UFH or LMWH for 6 weeks.^{7,18,125,169} Opinions vary in similar groups of women who undergo vaginal delivery.

REGIONAL ANESTHETIC CONSIDERATIONS

There have been reports in the literature of hematoma formation in the epidural space in nonpregnant patients treated with LMWH. The majority of these patients were elderly individuals who were also treated with nonsteroidal anti-inflammatory drugs, which impair platelet aggregation and subsequently affect platelet function. It has been accepted along with our anesthetic colleagues that the following guidelines be followed

when LMWH are used during pregnancy.

Epidural catheter and spinal anesthesia should be delayed for 10-12 hours after the last dose of LMWH in patients receiving prophylactic doses of LMWH.¹⁷⁶ In patients receiving full-dose anticoagulation, catheter placement or spinal anesthesia should not be performed for a minimum of 24 hours after the last dose of LMWH.¹⁷⁶ Prophylactic doses of LMWH should be withheld for 12 hours before induction of labor or cesarean section, and full dosing should be withheld for 24 hours before induction or cesarean delivery.^{172,176} Patients on LMWH should receive the next dose of LMWH (full anticoagulation) 10-12 hours after removal of the epidural/spinal catheter.¹⁷⁶ Two studies involving more than 80 patients showed no complications when using the established recommendations of not placing the epidural catheter until 12-24 hours after the last dose and not giving the next dose of LMWH until 10-12 hours after the removal of the epidural or spinal catheter.^{174,188} Furthermore, no complications were reported following this approach in a prospectively evaluated cohort of 180 patients managed with LMWH.¹⁷² However, the sample sizes of these studies may be insufficient to draw firm conclusions on the rare risk of epidural or spinal hematoma. With UFH, the timing of insertion and removal of the epidural catheter, as well as timing of cesarean delivery and the heparin dose, should be adjusted to avoid epidural anesthesia during peak heparin concentrations to reduce the risk of epidural hematoma.³⁶

CONSENSUS PANEL RECOMMENDATIONS FOR REGIONAL ANESTHESIA

- Withhold treatment with LMWH (prophylactic or full dosing) for 12 or 24 hours, respectively, before induction of labor or elective cesarean delivery, respectively.^{172,174,176,188} (Level II-1A)
- Start LMWH therapy 10-12 hours after removing the epidural catheter,

based on bleeding and physical examination.^{172,174,176,188} (Level II-1A)

- If necessary, induce labor at term (39 weeks) secondary to past obstetric history and the patient's desire for regional anesthesia. Counsel the patient in advance that regional anesthesia may not be an option if labor starts earlier. Be aware that induction can prolong labor (independent of risk factor for VTE) and can increase the risk for cesarean delivery (risk factor for VTE and for hemorrhage when anticoagulation is necessary in the postpartum period). (Level IIIC)
- Use endotracheal intubation with central induction of anesthesia in patients requiring cesarean delivery who received doses of LMWH before 12 hours (prophylactic) or before 24 hours (therapeutic). (Level IIIC)

PEDIATRIC/NEONATAL CONSIDERATIONS

Understanding the pathophysiology of poor pregnancy outcomes and of treatments designed to prevent maternal risk will benefit the fetus; however, there is minimal information regarding long-term fetal outcomes. Several lines of evidence suggest a role for thrombophilia and thrombosis in pregnancies associated with IUGR, fetal loss, placental abruption, and preeclampsia.^{56,80,82,97-111} Fetal thrombotic vasculopathy has been observed both in the placentas of such pregnancies and in neonates with neonatal encephalopathy.¹⁸⁹ A small case series has suggested an association between placental infarcts and neonatal thrombosis.¹⁹⁰ Further evidence of thrombotic cause has been suggested by elevated thrombin generation *in vivo*, measured by TATs, in women with pregnancies affected by IUGR or preeclampsia compared with women with normal pregnancies.¹⁹¹ Although the prevalence of thrombophilic conditions is greater in infants with thrombosis compared with the normal population, thrombosis is rare in neonates with thrombophilia who do not have additional risk factors (such as central venous catheters, cardiac disease, septicemia, dehydration, polycythemia, a diabetic mother).^{192,193} Oc-

casional thrombotic events, occurring as a result of IgG antibodies crossing the placenta, have been reported in infants of mothers with antiphospholipid antibodies.¹⁹⁴ These findings suggest that inherited thrombophilia in the infant contributes to, but is not the sole cause of, thrombotic complications; the question of whether fetal thrombophilia is a risk factor for poor pregnancy outcomes is controversial. Several large studies of pregnancy outcomes associated with maternal thrombophilia have reported conflicting results regarding pregnancy outcomes and there have been no long-term follow-up studies of the infants from such pregnancies.^{56,58,80,82,84-95}

On the basis of the evidence that thrombosis is a significant factor in poor pregnancy outcomes, clinical trials have been performed by using prophylaxis with UFH and LMWH or full anticoagulation during pregnancy in women with previous APO.^{114,138,139} However, no long-term follow-up of the infants was reported in these studies. The use of UFH or LMWH instead of warfarin is clearly advantageous for the fetus, because warfarin anticoagulation during pregnancy is associated with an increased risk of warfarin-induced embryopathy and an increased risk of fetal intracranial hemorrhage.¹²⁻¹⁵ It is unknown whether paternal inheritance of thrombophilia in the infant contributes to poor pregnancy outcomes, although a large Canadian study suggested that this is not a significant risk factor.⁵⁹ Most investigators agree that infants born to thrombophilic mothers or fathers may benefit from screening for the parental defect in order to guide future prophylactic measures to prevent thrombosis in the child. However, it should be noted that there are significant ramifications of screening in terms of unwarranted medical interventions and insurance coverage. The option of screening should be discussed with the parents. To augment effective counseling of future pregnancies and perinatal outcomes, a pathologist should examine the placenta and umbilical cord in at-risk pregnancies. Furthermore, evaluation and prompt treatment of additional risk factors, such as asphyxia, polycythemia, dehydration,

septicemia, and cardiac disease, may be warranted. In addition, affected infants who require central venous catheters should be considered for prophylactic anticoagulation with low-dose UFH.

CONSENSUS PANEL RECOMMENDATIONS FOR MANAGEMENT OF INFANTS IN AT-RISK PREGNANCIES

- Maternal anticoagulation with warfarin prior to delivery of the infant should be avoided where possible.¹²⁻¹⁴ (Level II-3A)
- Although not supported by the National Society of Genetic Counselors, the working group panel believes that infants of parents with known thrombophilic conditions may be screened for the thrombophilic risk factor after discussion of the potential ramifications with the parents. (Level IIIC)
- To augment effective counseling of future pregnancies and perinatal outcomes, a pathologist should examine the placenta and umbilical cord in at-risk pregnancies. (Level IIIC)
- Evaluation, and prompt treatment, of additional risk factors for thrombosis may be warranted. Such factors include asphyxia, polycythemia, dehydration, septicemia, and cardiac disease. Affected infants who require central venous catheters should be considered for prophylactic anticoagulation with low-dose UFH. (Level IIIC)

SUMMARY

Thrombophilia and the development of VTE during pregnancy can have very serious repercussions for both mother and fetus. Although a variety of antithrombotic treatments are available for the nonpregnant population, all have limitations in pregnant women. The management of thromboprophylaxis during pregnancy entails extensive patient and clinician interaction. Treatment plans have to be individualized, and require frequent modification over the course of the pregnancy as well as during labor and delivery and in the postpartum. There is a need for clear and concise guidance on the management of pregnant women

who are at risk of VTE or APOs. We have provided step-by-step recommendations for pregnant women with a variety of indications for thromboprophylaxis and treatment. However, these guidelines are based largely on level II and III evidence, or have been extrapolated from the nonpregnant population. We hope that, in the future, the prognosis for these women will be improved by the acquisition of data from large-scale, prospective, randomized studies. ■

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