REVIEW ARTICLE

CURRENT CONCEPTS

Venous Thromboembolic Disease and Pregnancy

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Pulmonary embolism and deep-vein thrombosis are the two components of a single disease called venous thromboembolism. Approximately 30% of apparently isolated episodes of pulmonary embolism are associated with silent deep-vein thrombosis, and in patients presenting with symptoms of deep-vein thrombosis, the frequency of silent pulmonary embolism ranges from 40 to 50%.[1,2] Venous thromboembolism is both more common and more complex to diagnose in patients who are pregnant than in those who are not pregnant. The incidence of venous thromboembolism is estimated at 0.76 to 1.72 per 1000 pregnancies, which is four times as great as the risk in the nonpregnant population.[3,4] A meta-analysis showed that two thirds of cases of deep-vein thrombosis occurred in the antepartum period and were distributed relatively equally among all three trimesters.[5] In contrast, 43 to 60% of pregnancy-related episodes of pulmonary embolism appear to occur in the puerperium.[4,6,7]

Pulmonary embolism is the leading cause of maternal death in the developed world. Current estimates of deaths from pulmonary embolism are 1.1 to 1.5 per 100,000 deliveries in the United States and Europe.[4,8,9] In the United Kingdom, venous thromboembolism accounts for one third of all maternal deaths.[8,9] Delayed diagnosis, delayed or inadequate treatment, and inadequate thromboprophylaxis account for many of the deaths due to venous thromboembolism.[8,9] Successful strategies for the management of venous thromboembolism in nonpregnant patients have been established. However, many of the recommendations for the treatment of pregnant patients who have venous thromboembolism are not based on high-quality data; rather, they are derived from observational studies and extrapolation from studies involving nonpregnant patients. The purpose of this review is to provide a practical approach to the diagnosis, management, and prevention of venous thromboembolism in pregnant patients.

Risk Factors for Venous Thromboembolism

Pregnancy is classically thought to be a hypercoagulable state. Fibrin generation is increased, fibrinolytic activity is decreased, levels of coagulation factors II, VII, VIII, and X are all increased, free protein S levels are decreased, and acquired resistance to activated protein C is common.[10] Uncomplicated pregnancy is accompanied by substantial hemostatic activation as indicated by increased markers of coagulation activation, such as prothrombin fragment F1+2 and D-dimer.[11] Also, reduction in venous flow velocity of approximately 50% occurs in the legs by 25 to 29 weeks of gestation and lasts until approximately 6 weeks after delivery, at which time it returns to normal nonpregnancy flow-velocity rates.[12,13] In addition, the presence of inherited thrombophilias and the antiphospholipid syndrome, as well as a previous history of thrombosis, increase the risk for venous thromboembolism during pregnancy and the postpartum period.[4]

Table 1. Estimated Prevalence of Congenital Thrombophilia and the Associated Risk of Thromboembolism during Pregnancy in a European Population.*

Risk Factor	Prevalence	Odds Ratio
	%	
Factor V Leiden mutation		
Heterozygous	2.0–7.0	9
Homozygous	0.2–0.5	34
Prothrombin G20210A mutation		
Heterozygous	2.0	7
Homozygous	Rare	26
Antithrombin deficiency (<80% activity)	<0.1–0.6	5
Protein C deficiency (<75% activity)	0.2–0.3	5
Protein S deficiency (<65% activity)	<0.1–0.1	3

* Data are from the Haemostasis and Thrombosis Task Force,[21] Robertson et al.,[22] and Nelson and Greer.[23]

Additional risk factors include black race, heart disease, sickle cell disease, diabetes, lupus, smoking, multiple pregnancy, age greater than 35 years, obesity, and cesarean delivery (especially emergency cesarean section during labor).[4,14-17] Because of their high prevalence, age greater than 35 years, obesity, and cesarean delivery contribute most substantially to rates of venous thromboembolism rates. There is a striking predisposition for deep-vein thrombosis to occur in the left leg (approximately 70 to 90% of cases), possibly because of exacerbation of the compressive effects on the left iliac vein due to its being crossed by the right iliac artery.[18] The incidence of isolated deep-vein thrombosis in the iliac vein is thought to be higher in pregnant women than in nonpregnant women. This complicates the diagnosis of deep-vein thrombosis in symptomatic pregnant women, because compression ultrasonography, the test of choice in nonpregnant subjects with suspected deep-vein thrombosis, does not reliably detect iliac deep-vein thrombosis. Isolated iliac-vein thrombosis may present with abdominal pain, back pain, and swelling of the entire leg; however, patients may also be asymptomatic and have no findings on physical examination.[19,20]

HERITABLE THROMBOPHILIA AND VENOUS THROMBOEMBOLISM

A thrombophilia is defined as a disorder of hemostasis that predisposes a person to a thrombotic event.[21] The prevalence of the inherited thrombophilias depends on the population studied (Table 1).[21-23] Data suggest that at least 50% of cases of venous thromboembolism in pregnant women are associated with an inherited or acquired thrombophilia.[24,25] In combination, the inherited thrombophilias are common (affecting 15% of Western populations) and underlie approximately 50% of cases of venous thromboembolism in pregnancy; however, venous thromboembolism occurs in only 0.1% of pregnancies. Therefore, the presence of a thrombophilia alone, even in the context of the hypercoagulable state of pregnancy, does not consistently result in a thrombotic event. Given the rarity of venous thromboembolism and the high incidence of inherited thrombophilias, universal screening of pregnant women is not cost-effective.[26,27] Thrombophilia screening is of limited value in women who have acute venous thromboembolism during pregnancy, because it does not alter the immediate clinical management of the disease, and both pregnancy and thrombosis affect the circulating level of many of the coagulation factors. However, thrombophilia screening should be considered after the end of pregnancy and once the use of anticoagulant agents has been stopped, since the results may affect the management of subsequent pregnancies.

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

Clinical suspicion is critical for the diagnosis of venous thromboembolism. However, many of the classic signs and symptoms of deep-vein thrombosis and pulmonary embolism, including leg swelling, tachycardia, tachypnea, and dyspnea, may be associated with a normal pregnancy. Common strategies for predicting pulmonary embolus have not been validated in pregnancy.[28] Venous thromboembolism is confirmed in less than 10% of pregnant women in whom the diagnosis is suspected, as compared with approximately 25% of nonpregnant patients.[29] However, since sudden death is not uncommon in pregnant patients who have features compatible with venous thromboembolism, all pregnant women with signs and symptoms suggestive of venous thromboembolism should have objective testing performed expeditiously. Treatment with low-molecular-weight heparin or unfractionated heparin is recommended until the diagnosis is ruled out by objective testing, unless treatment is strongly contraindicated.[30]

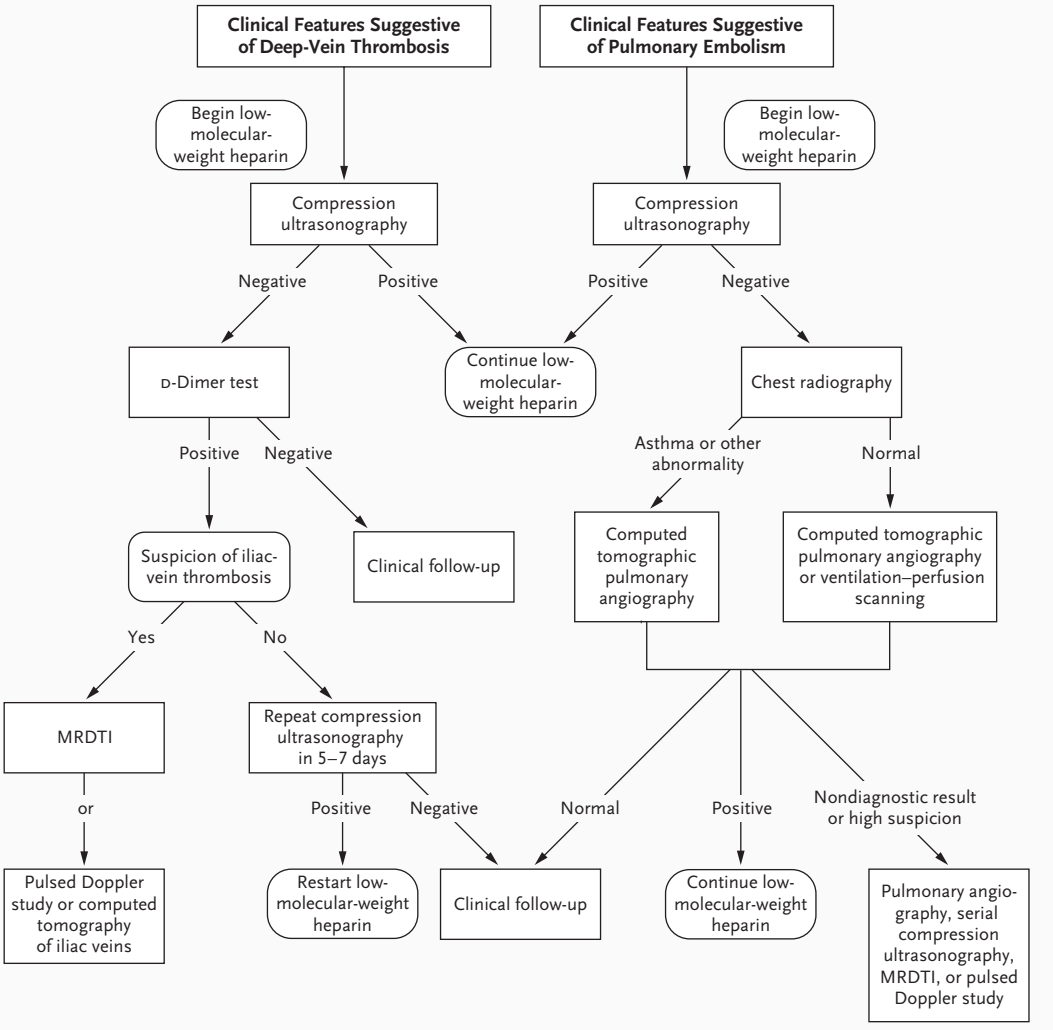

Figure 1. Diagnostic Algorithm for Suspected Deep-Vein Thrombosis and Pulmonary Embolism during Pregnancy.
If compression ultrasonography was negagive, low-molecular-weight heparin was discontinued. MRDTI denotes magnetic resonance direct thrombus imaging.

Compression ultrasonography is a noninvasive test with a sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal deep-vein thrombosis in the general population.[31] This test is without risk and is the test of choice in pregnant patients with suspected venous thromboembolism (Fig. 1). Compression ultrasonography is less accurate for isolated calf- and iliac-vein thrombosis.[32] During ultrasonography, the need for high pressure to compress the femoral vein in the groin or the absence of flow on Doppler studies is suggestive of iliac-vein thrombosis. Magnetic resonance direct thrombus imaging, which does not involve radiation exposure and is not harmful to the fetus, has a high sensitivity and specificity for the diagnosis of iliac-vein thrombosis.[20,33] A pulsed Doppler study of the iliac vein and computed tomographic (CT) scanning may be useful for detecting iliac-vein thrombosis when magnetic resonance imaging (MRI) is not available.[34,35] CT scanning, unlike either ultrasonography or MRI, is associated with fetal radiation exposure.

Levels of D-dimer increase with the progression of a normal pregnancy. However, the interpretation of the D-dimer level depends on which test is used to perform the assay and the cutoff values used. Current recommendations suggest that a D-dimer test should be used in combination with other tests.[30,36] Chan and coworkers showed that a negative test with a highly specific assay in the first and second trimesters had a negative pre-

Table 2. Recommended Initial Dose of Low-Molecular-Weight Heparin for the Treatment of Venous Thromboembolism According to Body Weight in Early Pregnancy.*

Low-Molecular-Weight Heparin	Body Weight in Early Pregnancy			
	<50 kg	50–69 kg	70–90 kg	>90 kg
Enoxaparin	40 mg twice a day	60 mg twice a day	80 mg twice a day	100 mg twice a day
Dalteparin	5000 U twice a day	6000 U twice a day	8000 U twice a day	10,000 U twice a day
Tinzaparin	175 U/kg once daily	175 U/kg once daily	175 U/kg once daily	175 U/kg once daily

* Data are from Bates et al.[29] and the Royal College of Obstetricians and Gynaecologists.[54]

dictive value of 100%; the sensitivity and specificity of a positive test were 100% and 60%, respectively.[37] However, a negative D-dimer test may not necessarily rule out venous thromboembolism.[38] A negative D-dimer test may be helpful if compression ultrasonography is normal, whereas a positive D-dimer test requires additional diagnostic testing.

Patients with suspected pulmonary embolism and normal findings on compression ultrasonography require additional diagnostic imaging (Fig. 1). A chest radiograph should be obtained to rule out alternative diagnoses and to guide further diagnostic testing. Ventilation–perfusion lung scanning or computed tomographic pulmonary angiography (CTPA) should be performed.[30] Ventilation–perfusion lung scanning delivers a higher fetal dose of radiation than does CTPA (640 to 800 μGy vs. 3 to 131 μGy); perfusion scanning alone will reduce the radiation exposure.[30,39,40] However, the radiation dose delivered to mothers is higher with CTPA than with scintigraphy (2.2 to 6.0 mSv vs. 1.4 mSv).[39,40] Women with suspected venous thromboembolism should be advised that ventilation–perfusion scanning carries a slightly higher risk of childhood cancer in offspring than does CTPA (1 case in 280,000 vs. <1 in 1 million) but carries a lower risk of maternal breast cancer (the lifetime risk is up to 13% greater with CTPA than with ventilation–perfusion scanning).[30]

MANAGEMENT OF VENOUS THROMBOEMBOLISM DURING PREGNANCY

The treatment and prophylaxis of venous thromboembolism in pregnancy center on the use of unfractionated heparin or low-molecular-weight heparin because of the fetal hazards associated with warfarin, which is known to cross the placenta.[41] Warfarin embryopathy is characterized by midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short phalanges; it affects 5% of fetuses that are exposed to the drug between 6 and 9 weeks of gestation.[42] The use of warfarin in the second trimester and early in the third trimester is associated with fetal intracranial hemorrhage and schizencephaly.[43,44] Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta, and thus there is no possibility of teratogenesis or fetal hemorrhage with these drugs.[45]

Although for many years unfractionated heparin was the standard anticoagulant used during pregnancy and into the puerperium, current guidelines now recommend low-molecular-weight heparin.[29,30,41] The advantages of low-molecular-weight heparin include a reduced risk of bleeding, predictable pharmacokinetics allowing weight-based dosing without the need for monitoring, and a reduced risk of heparin-induced thrombocytopenia and heparin-induced osteoporotic fractures.[29,46-48] The management of isolated calf-vein thrombosis is controversial, with no established guidelines. However, since most iliofemoral thromboses originate from calf-vein thromboses, full anticoagulation with low-molecular-weight heparin is suggested for symptomatic patients. The use of retrievable vena caval filters should be considered only for patients in whom anticoagulation is contraindicated or in whom extensive venous thromboembolism develops within 2 weeks before delivery.[49]

In the nonpregnant patient with venous thromboembolism, low-molecular-weight heparin is usually administered once daily with the use of a weight-adjusted dose regimen. Opinion is divided as to the optimal regimen for low-molecular-weight heparin in pregnant women. Because of

increased renal excretion, the half-life of low-molecular-weight heparin decreases in pregnancy.[50,51] Consequently, a twice-daily weight-based regimen has been recommended[29,30,41,46,52,53] (Table 2); however, many clinicians use once-daily dosing to simplify administration. Clinical experience suggests that in most patients, monitoring anti–factor Xa activity and making dose adjustments are not required except in patients at the extremes of body weight and those with altered renal function.[52,53]

Cutaneous allergic reactions to low-molecular-weight heparin are rare and include pruritus, urticarial rashes, erythematous plaques, and very rarely, skin necrosis. These reactions are reported to be more common during long-term use in pregnant women than during short-term use in nonpregnant persons.[55,56] Cross-reactivity occurs in about a third of women who are switched from one preparation of low-molecular-weight heparin to another. Limited experience with fondaparinux, a synthetic pentasaccharide and direct inhibitor of factor Xa, suggests that it may be a safe alternative in women with cross-reactivity among several low-molecular-weight heparins.[57] Although placental transfer of fondaparinux was not observed in an in vitro model,[58] limited clinical experience suggests that fondaparinux passes the placental barrier in vivo, resulting in low but measurable anti–factor Xa activity in umbilical-cord blood.[59] The Food and Drug Administration has designated fondaparinux as being in pregnancy category B (i.e., reproduction studies in animals have failed to demonstrate a risk to the fetus, and there are no data from adequate and well-controlled studies involving pregnant women).

Bed rest is generally not recommended for patients with deep-vein thrombosis, except for those with phlegmasia.[60] Low-risk, nonpregnant patients with deep-vein thrombosis have been treated successfully with low-molecular-weight heparin on an outpatient basis.[61] Such an approach can be considered in selected pregnant patients.

ANTICOAGULANT THERAPY DURING LABOR AND DELIVERY

The management of anticoagulation at the end of pregnancy is challenging, since the onset of labor is not predictable and both vaginal delivery and cesarean delivery are associated with blood loss and are frequently conducted with the patient under regional anesthesia. If spontaneous labor occurs in women who have undergone full anticoagulation, neuraxial anesthesia should not be used because of the risk of spinal hematoma.[29,62] This problem can be overcome by scheduling elective induction of labor or cesarean section.

Current guidelines of the American Society of Regional Anesthesia and Pain Medicine suggest that spinal anesthesia may be performed 12 hours after administration of the last dose of prophylactic low-molecular-weight heparin and 24 hours after the last dose of therapeutic low-molecular-weight heparin (given either once or twice daily).[63] Intravenous unfractionated heparin should be stopped 6 hours before placement of a neuraxial blockade, and a normal activated partial-thromboplastin time should be confirmed.[63] Women who continue taking low-molecular-weight heparin should be advised that once they are in established labor, no further heparin should be taken. Because of the relatively high chance of cesarean delivery and the difficulty in predicting the onset of labor, many obstetricians are reluctant to treat a woman with low-molecular-weight heparin all the way through her pregnancy, since the agent's effects cannot be expeditiously reversed. Patients commonly are switched to subcutaneous unfractionated heparin for the last few weeks of pregnancy, although the benefit of this approach has not been validated by clinical studies. However, since the pharmacokinetics and pharmacodynamics of subcutaneous unfractionated heparin are unpredictable during the third trimester of pregnancy, meticulous monitoring of the activated partial-thromboplastin time, with dosage adjustment as needed, is required.[64] Furthermore, contrary to popular belief, the pharmacokinetics of subcutaneous unfractionated heparin and low-molecular-weight heparin are quite similar.[65] These factors, together with the safety concerns regarding the use of unfractionated heparin, limit the benefit of this approach.[66]

Treatment with low-molecular-weight heparin may be resumed within 12 hours after delivery in the absence of persistent bleeding.[41] The initiation of prophylactic low-molecular-weight heparin should be delayed for at least 12 hours after the removal of an epidural catheter.[63] After neuraxial anesthesia, therapeutic low-molecular-weight heparin should be administered no ear-

lier than 24 hours postoperatively or post partum and in the presence of adequate hemostasis.[63] Anticoagulation therapy with either low-molecular-weight heparin or warfarin is recommended for at least 6 weeks post partum and for a total of at least 6 months.[29] Before treatment is discontinued, the risk of thrombosis should be assessed. The post-thrombotic syndrome occurs in up to 60% of patients after a deep-vein thrombosis and is a cause of serious complications.[67,68] Compression stockings reduce the risk of the post-thrombotic syndrome by about 50% and should be worn on the affected leg for up to 2 years after the acute event.[30,68]

THROMBOLYTIC THERAPY

Although experience with thrombolytic therapy in pregnancy is limited, the use of thrombolytic agents may be lifesaving in patients with massive pulmonary embolism and severe hemodynamic compromise.[69] There is concern that thrombolytic therapy will lead to placental abruption, but this complication has not been reported. Although thrombolytic therapy within 10 days after cesarean section or delivery is contraindicated, successful thrombolysis has been reported within 1 hour after vaginal delivery and within 12 hours after cesarean section.[70]

MANAGEMENT OF PULMONARY EMBOLISM IN LATE PREGNANCY AND LABOR

Patients presenting with pulmonary embolism in late pregnancy should be treated with supplemental oxygen (to achieve an oxygen saturation of >95%) and intravenous heparin and should be transferred to a major medical center that has a maternal–fetal, neonatal, and cardiothoracic unit for high-risk patients. In hemodynamically stable patients, a temporary vena caval filter should be placed once the diagnosis has been confirmed.[49] As soon as the patient goes into active labor or a cesarean section is considered, the heparin should be stopped (and reversed with protamine if necessary). A cesarean section should not be performed while the patient is in a fully anticoagulated state; this can lead to uncontrolled bleeding and maternal death.

The care of the pregnant patient who has massive pulmonary embolism either at term or when suspicion of compromised fetal status would call for expeditious cesarean delivery is complex and requires a coordinated treatment strategy by the obstetrician, intensivist, cardiothoracic surgeon, anesthesiologist, and interventional radiologist. The approach to the management of a massive pulmonary embolism should be individualized and adapted to changing circumstances; it could include cardiopulmonary bypass with surgical embolectomy followed by cesarean section or percutaneous mechanical clot fragmentation and placement of an inferior vena caval filter. Although thrombolytic therapy is considered to be contraindicated, successful outcomes with the use of thrombolytic therapy during labor have been reported.[71,72]

THROMBOPROPHYLAXIS DURING PREGNANCY AND THE PUERPERIUM

Women who have had a thromboembolic event have a much higher risk of a recurrent episode during pregnancy than women without such a history.[73,74] The risks of venous thromboembolism are even higher in the puerperium. Graduated compression stockings are recommended ante partum and post partum for all women who have had a previous venous thromboembolism.[29] Similarly, postpartum pharmacologic thromboprophylaxis for at least 6 weeks (low-molecular-weight heparin or warfarin) is recommended for all women who have had a previous venous thromboembolism.[29] Aspirin is not recommended for thromboprophylaxis.[75]

The indications for antepartum pharmacologic prophylaxis are more controversial,[23,29,76] and the risks and benefits should be evaluated for each patient, with the patient involved in the decision-making process. Pregnant women with two or more previous episodes of venous thromboembolism and those with high-risk thrombophilias (e.g., antithrombin deficiency, the antiphospholipid syndrome, compound heterozygosity for prothrombin G20210A variant and factor V Leiden, or homozygosity for prothrombin G20210A variant or factor V Leiden), regardless of whether they have a history of venous thromboembolism, should receive antenatal thromboprophylaxis (Table 3).[29] Antenatal anticoagulation may not be required for women whose previous venous thromboembolism was not related to pregnancy and was associated with a risk factor that is no longer present, as long as such women do not have additional risk factors or thrombophilia.[54,73,74,76,77]

Table 3. Recommended Antenatal Prophylactic Doses of Low-Molecular-Weight Heparin According to Body Weight and Risk.*

Low-Molecular-Weight Heparin	Body Weight			Very High Risk
	<50 kg	50–90 kg	>90 kg	
Enoxaparin	20 mg daily	40 mg daily	40 mg every 12 hr	0.5–1.0 mg/kg every 12 hr
Dalteparin	2500 U daily	5000 U daily	5000 U every 12 hr	50–100 U/kg every 12 hr
Tinzaparin	3500 U daily	4500 U daily	4500 U every 12 hr	4500 U every 12 hr

* Data are from Bates et al.[29] and the Royal College of Obstetricians and Gynaecologists.[30]

Table 4. Risk Assessment for Thromboembolism in Patients Who Undergo Cesarean Section.*

Low risk: early ambulation
Cesarean delivery for uncomplicated pregnancy with no other risk factors
Moderate risk: low-molecular-weight heparin or compression stockings
Age >35 yr
Obesity (BMI >30)
Parity >3
Gross varicose veins
Current infection
Preeclampsia
Immobility for >4 days before operation
Major current illness
Emergency cesarean section during labor
High risk: low-molecular-weight heparin and compression stockings
Presence of more than two risk factors from the moderate-risk section
Cesarean hysterectomy
Previous deep-vein thrombosis or known thrombophilia

* BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

For pregnant women with a single idiopathic episode of venous thromboembolism and for those with a single previous venous thromboembolism and a low-risk thrombophilia, antenatal thromboprophylaxis is considered optional, although close clinical surveillance throughout pregnancy is essential for those women who opt not to receive thromboprophylaxis.[29] Thromboprophylaxis should also be considered for morbidly obese patients (body-mass index [the weight in kilograms divided by the square of the height in meters], >40) and those confined to bed, particularly if other risk factors are also present.[9]

THROMBOPROPHYLAXIS AFTER CESAREAN SECTION

Venous thromboembolism after cesarean section is uncommon but causes serious complications and may be fatal. The incidence of pulmonary embolism is reported to be higher after cesarean section than after vaginal delivery, by a factor of 2.5 to 20, and the incidence of fatal pulmonary embolism by a factor of 10.[78,79] According to the Confidential Enquiry into Maternal Death in the United Kingdom, more than three quarters of the postpartum deaths caused by venous thromboembolism were associated with cesarean delivery.[8,78] Although adequately powered prospective, randomized, controlled studies have shown thromboprophylaxis to be highly effective in reducing the incidence of venous thromboembolism after moderate-to-high-risk general, urologic, and gynecologic surgery, no such studies have been performed after cesarean section.[75] The Royal College of Obstetricians and Gynaecologists and the American College of Chest Physicians provide recommendations for risk assessment and thromboprophylaxis after cesarean section (Table 4).[29,80]

To our knowledge, the duration of thromboprophylaxis after cesarean section has not been studied. This issue is particularly important in view of the practice of early discharge from the hospital after a cesarean section, since the overall incidence of peripartum deep-vein thrombosis is highest during the first postpartum week.[3] The decision to use thromboprophylaxis should be made on the basis of each patient's risk assessment, with continuation of low-molecular-weight heparin and the use of compression stockings for up to 6 weeks in selected high-risk patients in whom important risk factors persist after delivery.[29] Other high-risk patients (e.g.,

those who are obese or have had an emergency cesarean delivery) could reasonably be discharged to home while continuing to take low-molecular-weight heparin for a brief period, although we are aware of no published studies that quantify the benefit of this approach.

No potential conflict of interest relevant to this article was reported.

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