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Prevention and management of venous thromboembolism in pregnancy

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Pulmonary thromboembolism (PTE) remains a major cause of maternal mortality in the developed world. In the United Kingdom [1], one of the few countries that comprehensively collect, review, and publish data on maternal deaths (http://www.cemd.org.uk/), PTE has been the most common direct cause of maternal mortality for many years. PTE arises from deep venous thrombosis (DVT), but many DVTs are not recognized before the occurrence of PTE. DVT also is associated with a significant risk of recurrent thrombosis, especially if there is an underlying thrombophilia, and deep venous insufficiency manifests as the postthrombotic syndrome. PTE carries a risk of subsequent pulmonary hypertension. Pregnancy-related venous thromboembolism (VTE) may identify women with an underlying thrombophilia that may be associated with an increased risk of pregnancy complications. Many of the maternal deaths from PTE are associated with substandard care [1], including failures to recognize risk factors for VTE, failures to provide appropriate thromboprophylaxis for those persons at risk, failures to diagnose VTE objectively, and failures to provide appropriate treatment.

Epidemiology of venous thromboembolism in pregnancy

The incidence of antenatal DVT varies with age. It has been estimated to be 0.615 event per 1000 maternities in women less than 35 years of age and 1.216 events per 1000 maternities in women more than 35 years of age [2]. The incidence of postpartum DVT has been estimated to be 0.304 event per 1000 maternities in women less than 35 years of age and 0.72 event per 1000 maternities in women more than 35 years of age. Although antenatal DVT is more common than postpartum DVT [2], the event rate is higher in the 6 weeks of the puerperium. Almost 40% of postpartum DVTs present following the woman's discharge from hospital. Complete data on postpartum DVT are difficult to obtain, because many cases present to nonobstetric services. The United Kingdom Confidential Enquiries provide accurate data for fatal PTE. Overall, the incidence of fatal PTE has fallen substantially from the early 1950s. The greatest reduction has occurred in the number of deaths following vaginal delivery. This decrease is probably related to the "demedicalization" of childbirth, with shorter stays inhospital, more rapid mobilization, and shorter labors. Nonetheless, in recent years, there has been no further reduction in fatalities after vaginal delivery [1], and the number of deaths during the antenatal period has changed little from the early 1950s despite major advances in the identification of risk, thromboprophylaxis, diagnosis, and therapeutics over this same period. The total number of deaths following cesarean section seems to have fallen sharply since the widespread introduction of specific thromboprophylaxis to United Kingdom clinical obstetric practice in the mid-1990s.

The major risk factors for VTE are increasing maternal age (particularly over 35 years), operative vaginal delivery, cesarean section (especially if carried out as an emergency in labor), a high body mass index, previous VTE (especially idiopathic or throm-

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bophilia associated), thrombophilia, and a family history of thrombosis suggestive of an underlying thrombophilia [3] (Table 1). The risk of VTE associated with ovarian hyperstimulation for assisted conception therapy is often overlooked. Hyperstimulation provokes procoagulant changes in the hemostatic and fibrinolytic systems. These changes can result in venous and arterial thrombosis, although the overall rate of thrombosis in assisted conception is low. When VTE occurs, it is usually in the internal jugular vein and presents with neck pain and swelling. A risk assessment for thrombosis should be undertaken in women undergoing assisted conception therapy and appropriate thromboprophylaxis provided for those at high risk.

Following DVT, there is a risk of deep venous insufficiency. A recent study found that more than 60% of women had objectively confirmed deep venous insufficiency following a treated DVT, and almost 80% experienced postthrombotic syndrome. The odds ratio for developing venous insufficiency after a DVT has been estimated at 10.9 (95% confidence interval [CI], 4.2–28.0) versus 3.8 (95% CI, 1.2–12.3) after a PTE [4]. The difference may be explained by thrombus clearing from the legs in women with PTE, leading to less extensive damage to the deep venous system. Another study has also illustrated the frequency of symptoms associated with the postthrombotic syndrome following DVT in pregnancy (Table 2) [5]. The risk of pulmonary hypertension has not been quantified for pregnancy-associated VTE.

Table 1
Common risk factors for venous thromboembolism in pregnancy

Patient factors	Pregnancy/obstetric factors
Age over 35 years	Ovarian hyperstimulation
Obesity (BMI > 29 kg/m^2)	Cesarean section, particularly
in early pregnancy	as an emergency in labor
Thrombophilia	Operative vaginal delivery
Past history of VTE	Major obstetric hemorrhage
(especially if idiopathic	
or thrombophilia	
associated)	
Gross varicose veins	Hyperemesis gravidarum
Significant current medical	Pre-eclampsia
problem (eg, nephrotic	
syndrome)	
Current infection or	
inflammatory process	
(eg, active inflammatory	
bowel disease or urinary	
tract infection)	
Immobility (eg, bed rest or	
lower limb fracture)	
Paraplegia	
Recent long distance travel	
Dehydration	
Intravenous drug abuse	

Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

Table 2
Subjective complaints in women followed up after pregnancy-associated deep venous thrombosis (DVT)

Parameter	DVT in pregnancy	DVT in puerperium
Number of women studied	61	33
Follow-up time (median)	10 years (range, 7–21)	11 years (range, 7–26)
Leg swelling	59%	48%
Varicose veins	36%	30%
Skin discoloration	28%	27%
Regular use of compression bandage	21%	3%
Leg ulcer	6.5%	0%

From Bergqvist D, Bergqvist A, Lindhagen A, et al. Long-term outcome of patients with venous thromboembolism during pregnancy. In: Greer IA, Turpie AGG, Forbes CD, editors. Haemostasis and thrombosis in obstetrics and gynaecology. London: Chapman and Hall; 1992. p. 349–59; with permission.

Pathogenesis of venous thromboembolism in pregnancy

Virchow's classic triad of factors underlying VTE, that is, hypercoagulability, venous stasis, and endothelial damage, occur in the course of normal pregnancy and delivery. Hypercoagulability results from the increased levels of coagulation factors, such as von Willebrand factor, factor VIII, and fibrinogen; from an acquired resistance to the endogenous anticoagulant, activated protein C, found in almost 40% of normal pregnancies; from a reduction in protein S, the cofactor for activated protein C [6]; and from impaired fibrinolysis through increases in plasminogen activator inhibitors 1 and 2, the latter being placentally derived [7]. High factor VIII levels and resistance to activated protein C are independently associated with an increased risk of VTE. Venous flow in the lower limbs is reduced by approximately 50% by the end of the second trimester, reaching a nadir at 36 weeks [8] and returning to normal nonpregnant flow rates at approximately 6 weeks postpartum. Endothelial damage to pelvic vessels can occur during the course of vaginal delivery or cesarean section.

More than 70% of DVTs in pregnancy are iliofemoral in contrast to their location in the nonpregnant situation, when the majority are calf vein thrombosis, with approximately 9% of DVTs being iliofemoral. Iliofemoral DVTs are more likely to embolize than are isolated calf vein thromboses. Almost 90% of DVTs affect the left side in pregnancy versus 55% in nonpregnant women [3,9]. This difference may be the result of compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein on the left side only.

Thrombophilia and venous thromboembolism in pregnancy

Thrombophilia is found in approximately 50% of women with a VTE during pregnancy. The major heritable forms of thrombophilia include deficiencies of the endogenous anticoagulant proteins, that is, antithrombin, protein C, and protein S; abnormalities of procoagulant factors, particularly factor V Leiden; and the prothrombin gene variant, prothrombin 20210A.

Hyperhomocysteinemia is associated with VTE in nonpregnant women [10] and may reflect underlying homozygosity for a variation in the methylenetetrahydrofolate reductase gene (MTHFR C677T), which occurs in approximately 10% of Western populations. This genotype is not directly linked to VTE and requires an interaction with dietary deficiency of B vitamins. In contrast to the nonpregnant situation, this genotype has not been associated with an increased risk of pregnancy-related VTE [11–13]. The lack of association in pregnancy may reflect the physiologic decrease in homocysteine levels seen in normal pregnancy or the effects of folic acid supplements.

Quantitative or qualitative deficiencies of the anticoagulant proteins antithrombin, protein C, and protein S [14] have a combined prevalence of less than 10 in 1000 in European populations (the true prevalence of protein S deficiency has not yet been clearly established), and, collectively, such deficiencies are found in less than 10% of cases of VTE.

Factor V Leiden produces resistance to activated protein C, the endogenous anticoagulant directed against factors Va and VIIIa. Activated protein C inhibits coagulation by proteolytic cleavage of these factors. With factor V Leiden, resistance to the activity of protein C is caused by a single point mutation in the factor V gene at the cleavage site where activated protein C acts. This defect results in a potentially hypercoagulable effect. Factor V Leiden has a prevalence of approximately 2% to 7% in Western Europeans [14] (the prevalence is much lower in other populations such as the Chinese) and can be identified in 20% to 40% of patients with VTE [15]. Activated protein C resistance can be caused by problems other than factor V Leiden, including antiphospholipid antibody syndrome and other genetic defects in the factor V molecule. It also can be acquired in pregnancy [6], possibly owing to increases in factors V and VIII. The prothrombin gene variant (prothrombin G20210A) is present in approximately 2% of the population. It is associated with elevated plasma prothrombin levels and increases the risk for VTE by threefold [16]. This variant is found in approximately 6% of patients with VTE and in 18% of patients with a family history of VTE [16]. It has been found in pregnancy-associated VTE [13,17]. Although factor V Leiden is associated with an increased risk for VTE, this risk is largely an increase in DVT. The prevalence of underlying factor V Leiden in PTE is approximately half of that in DVT. In contrast, in other thrombophilias such as prothrombin G20210A, there is no difference in the underlying prevalence of DVT and PTE. Factor V Leiden may be associated with a more adherent and stable thrombus, possibly owing to increased local thrombin generation, reducing the likelihood of embolization. Whether this effect occurs in pregnant women with factor V Leiden is not clear.

Heritable causes [18,19] are present in at least 15% of Western populations and underlie approximately 50% of episodes of VTE in pregnancy (Table 3). Nonetheless, the incidence of VTE in pregnancy is only 1 in 1000. The presence of a thrombophilia, even when combined with the prothrombotic changes in coagulation and venous flow found in pregnancy, does not usually result in VTE. VTE in women with thrombophilia reflects a multicausal event resulting from the interaction between congenital and acquired risk factors [19]. The level of risk depends on the underlying thrombophilic defects, the history of thrombotic events, and addi-

Table 3
Typical prevalence rates for congenital thrombophilia in European populations

Thrombophilic defect	Prevalence (%)
Antithrombin deficiency	0.25–0.55
Protein C deficiency	0.20–0.33
Factor V Leiden heterozygotes	2–7
Prothrombin G20210A heterozygotes	2
MTHFR C677T homozygotes	10

Abbreviations: MTHFR, methylene-tetrahydrofolate reductase.

tional risk factors (see Table 1). One must establish the risk of thrombosis in pregnant women with thrombophilia to guide thromboprophylaxis.

Initial estimates of the risk for VTE in pregnant women with thrombophilia without thromboprophylaxis were high. The rates were estimated to be as high as 60% in antithrombin-deficient women [14,20], 3% to 10% in protein C deficiency, and 0% to 6% in protein S deficiency [14,20]; however, these data were obtained from observational studies of symptomatic thrombophilic kindreds. This type of study overestimates the risk in asymptomatic kindreds. Factor V Leiden has been found in as many as 46% of women investigated for VTE in pregnancy [21], but, again, this finding reflects the investigation of symptomatic women. Recent studies have provided estimates of the risk for VTE in pregnancy in women with the more common thrombophilias. Gerhardt et al [12] reported a relative risk for VTE in pregnancy after adjusting for other key variables of 6.9 (95% CI, 3.3–15.2) with factor V Leiden, 9.5 (95% CI, 2.1–66.7) with prothrombin G20210A, and 10.4 (95% CI, 2.2–62.5) with antithrombin deficiency. Combined defects (including homozygous thrombophilias) substantially increased the risk, with an odds ratio estimated at 107 for the combination of factor V Leiden and prothrombin G20210A in pregnancy. Additional risk factors, such as obesity, were present in 25% of the cases versus 11% of controls. Women with recurrent VTE were more likely to have underlying combined thrombophilic defects, protein C or antithrombin deficiency, or prothrombin G20210A. The study by Gerhardt and co-workers also provided a positive predictive value for each thrombophilia, assuming an underlying rate of VTE of 0.66 per 1000 pregnancies, consistent with estimates from Western populations [18]. These values were 1 in 500 for factor V Leiden, 1 in 200 for prothrombin G20210A, and 4.6 in 100 for these defects combined. These data are supported by a retrospective study of 72,000 pregnancies in women with VTE who were assessed for thrombophilia [4] and in whom the underlying prevalence of these defects in the population was known. The risk of thrombosis was 1 in 437 for factor V Leiden, 1 in 113 for protein C deficiency, 1 in 2.8 for type 1 (quantitative) antithrombin deficiency, and 1 in 42 for type 2 (qualitative) antithrombin deficiency. This study was recently extended [13], reporting an odds ratio of 4.4 (95% CI, 1.2–16) for prothrombin G20210A, 4.5 (95% CI, 2.1–14.5) for factor V Leiden, 282 (95% CI, 31–2532) for antithrombin deficiency type 1 (quantitative deficiency), and 28 (95% CI, 5.5–142) for antithrombin deficiency type 2 (qualitative deficiency). More recently, Martinelli et al [22] reported a case–control study of 119 women with a

Table 4
Risk of venous thromboembolism in pregnant women with thrombophilia

Thrombophilia	Odds ratio (95% CI) for VTE in pregnancy[a]	Relative risk (95% CI) for VTE in pregnancy[b]	Relative risk (95% CI) for VTE in pregnancy or puerperium[c]
AT deficiency type 1 (quantitative deficiency)	282 (31–2532)	NA	NA
AT deficiency type 2 (qualitative deficiency)	28 (5.5–142)	NA	NA
AT deficiency (activity <80%)	NA	10.4 (2.2–62.5)	NA
Factor V Leiden heterozygotes	4.5 (2.1–14.5)	6.9 (3.3–15.2)	8.7 (3.4–22.5)
Prothrombin G20210A heterozygotes	4.4 (1.2–16)	9.5 (2.1–66.7)	1.8 (0.6–5.4)
MTHFR C677T homozygotes	0.45 (0.13–1.58)	No increase in risk (relative risk not reported)	NA
Any thrombophilia	NA	NA	9.0 (4.7–17.1)
Antithrombin, protein C, or protein S deficiency (not adjusted for parity)	NA	NA	13.1 (5.0–34.5)

Abbreviations: AT, antithrombin; CI, confidence interval, MTHFR, methylenetetrahydrofolate reductase; NA, not available; VTE, venous thromboembolism.

[a] Based on a retrospective study of 93,000 pregnancies in which the odds ratios were calculated by screening women with VTE in pregnancy for thrombophilia and relating this to the known prevalence of these defects in the population [12].

[b] Based on a study of 119 women with thromboembolism in pregnancy and 233 controls for the presence of congenital thrombophilia [12]. Relative risk was calculated after logistic regression to adjust for age, body mass index, oral contraceptive use, protein C and S activity, factor V Leiden, prothrombin G20210A, MTHFR 677TT, and antithrombin activity.

[c] Based on a case–control study of 119 women who had a first episode of objectively confirmed VTE in pregnancy or the puerperium and 232 controls. Relative risk was adjusted for parity. No difference was noted between relative risk in pregnancy or puerperium [22].

first episode of VTE during pregnancy or the puerperium. The relative risk for VTE was 10.6 (95% CI, 5.6–20.4) for heterozygotes of factor V Leiden, 2.9 (95% CI, 1.0–8.6) for prothrombin G20210A heterozygotes, and 13.1 (95% CI, 5.0–34.2) for protein C, protein S, and antithrombin deficiency grouped together. These data are valuable in evaluating risk and in advising women whether to use thromboprophylaxis in pregnancy (Table 4).

Currently, there is no evidence to support a policy of routine universal screening for thrombophilia in pregnancy. The natural history of many of these conditions, particularly in asymptomatic women, has not been fully established, and the need for and the type of intervention are not established. The author and his colleagues have recently assessed the cost-effectiveness of screening for factor V Leiden in pregnancy and have found that universal screening is not cost-effective (Table 5) [23]. There is a stronger argument for selective screening of women with a personal or family history of VTE, because a thrombophilia will be found in approximately 50% of cases [18]. There is a consensus that women with a personal history of VTE and an underlying thrombophilia should receive specific thromboprophylaxis during pregnancy, particularly in the puerperium [24]. Screening for thrombophilia in patients with problems such as recurrent miscarriage, intrauterine death, severe and recurrent intrauterine growth restriction, or pre-eclampsia should also be considered in view of the evidence linking thrombophilia with these pregnancy complications [18]. If screening is to be employed in these situations, appropriate interventions must be identified.

Recurrent venous thromboembolism in pregnancy

There is a consensus that women with more than one previous VTE should receive antenatal thromboprophylaxis. The management of the woman with a single previous VTE has been more controversial because of the wide variation in reported risk, ranging from 1% to 13% [24–28], and the side effects of unfractionated heparin in pregnancy. Nevertheless, these studies have the following limitations: objective testing was not used in all of the cases; some of the studies were retrospective; and the prospective studies had relatively small sample sizes. Brill-Edwards et al [29] recently provided valuable data for the management of such women. They prospectively studied 125 pregnant women with a single previous objectively diagnosed VTE. No heparin was given antenatally, but anticoagulant therapy, usually warfarin following an initial short course of heparin or low molecular weight heparin (LMWH), was given for 4 to 6 weeks postpartum. The overall antenatal recurrence rate was 2.4% (95% CI, 0.2–6.9). There were no episodes of recurrent VTE in the 44 women (95% CI, 0–8.0) who did not have an underlying thrombophilia and whose previous VTE had been associated with a temporary risk factor. The temporary risk factors were pregnancy in 35%, oral contraceptive use in 23%, surgery in 18%, trauma in 14%,

Table 5
Cost-effectiveness of screening for factor V Leiden in pregnancy

	No screening (n = 967)	Selective screening (n = 113)	Universal screening (n = 967)
Cost of screening for mutation	0	£1305.31	£11,543.29
Cost of prophylactic postpartum LMWH for those positive for FVL	0	£595.48	£5959.80
Cost of prophylactic LMWH (from 12–40 weeks' gestation) for those positive for FVL	0	£2774.94	£27,787.20
Averted costs of treating vascular events (assumes 50% reduction with prophylaxis)	0	£908.13	£5448.81
Net cost of treatment for whole cohort	£158,013.4	£157,105.3	£152,566.6
Total cost of management strategy	£158,013.4	£161,781.0	£197,856.9
Number of women identified with FVL	0	3	30
Number of women with complications possibly associated with FVL	87	1	6
Events prevented by screening (assumes 50% reduction with prophylaxis)	0	0.5	3

Abbreviations: FVL, factor V Leiden; LMWH, low molecular weight heparin.
From Clark P, Twaddle S, Walker ID, Scott L, Greer IA. Screening for the factor V Leiden mutation in pregnancy is not cost effective. Lancet 2002;359:1919–20; with permission.

immobility in 4%, and chemotherapy in 1%. In contrast, women who were found to have an underlying thrombophilia or whose previous VTE was idiopathic had an antepartum recurrence rate of 5.9% (95% CI, 1.2–16). These data suggest that women with a single previous event associated with a temporary risk factor and who do not have identifiable thrombophilia should not routinely receive heparin or LMWH antenatally. Nonetheless, given the wide confidence intervals and the implications of a further event, this decision should be discussed with the patient and her wishes taken into account. In women with an underlying thrombophilia or in whom VTE is idiopathic, there is a much stronger argument for pharmacologic thromboprophylaxis.

Diagnostic issues regarding venous thromboembolism in pregnancy

The clinical features of DVT include leg pain or discomfort (especially on the left side), swelling, tenderness, increased temperature and edema, lower abdominal pain, mild pyrexia, and an elevated white blood cell count. Women presenting with abdominal pain, leukocytosis, and pyrexia can be misdiagnosed as sustaining intra-abdominal pathology such as appendicitis. Features suggestive of PTE include dyspnea, collapse, chest pain, hemoptysis, faintness, raised jugular venous pressure, and focal signs in the chest, sometimes combined with the symptoms and signs of DVT. As is true in the nonpregnant patient, the clinical diagnosis of VTE during pregnancy is unreliable, particularly because problems such as leg swelling and discomfort are common features of normal pregnancy. In a study of consecutive pregnant women presenting with a clinical suspicion of DVT, the diagnosis was confirmed in less than 10% [24]. In contrast, approximately 25% of diagnoses are confirmed in the nonpregnant patient [30–32]. Approximately 30% of nonpregnant patients presenting with possible PTE have the diagnosis confirmed [33,34], but the number of positive results following investigation seems to be substantially lower in pregnancy [24], reflecting a low threshold for investigation. An objective diagnosis of VTE in pregnancy is essential, because the failure to identify a VTE will endanger the mother, and unnecessary treatment will expose her to the hazards of anticoagulation.

Real-time or duplex ultrasound venography is the main diagnostic tool [35] to detect DVT. If DVT is confirmed, anticoagulant treatment should be commenced or continued. In nonpregnant subjects, the pretest clinical probability of DVT modifies the positive predictive value and the negative predictive value of objective diagnostic tests [36,37]. Applying this principle to pregnancy, a negative ultrasound result with a low level of clinical suspicion suggests that anticoagulant treatment can be discontinued or withheld. In the presence of a negative ultrasound report and a high level of clinical suspicion, the woman should be anticoagulated and ultrasound repeated in 1 week, or alternative imaging techniques such as x-ray venography or MRI should be considered. If repeat testing is negative, anticoagulant treatment should be discontinued [38].

In the woman with suspected PTE, a ventilation–perfusion lung scan and bilateral duplex ultrasound leg examinations should ideally be performed. In the nonpregnant woman, a normal perfusion scan has a negative predictive value of over 99% and a high-probability lung scan a positive predictive value of over 85%. When there is a strong clinical suspicion of PTE, the positive predictive value of a high-probability lung scan increases to over 95%, whereas with low clinical probability, it decreases to under 60%.

The greatest diagnostic problem is when the ventilation–perfusion scan is in the medium range. In practical terms, when the scan suggests a "medium" or "high" probability of PTE, or when there is a "low" probability of PTE on a ventilation–perfusion scan but a positive result on ultrasound for DVT, anticoagulant treatment should be continued. When a ventilation–perfusion scan suggests a low risk for PTE and there are negative leg ultrasound examinations in a patient in whom there is a high level of clinical suspicion, anticoagulant treatment should be continued with repeat testing in 1 week (ventilation–perfusion scan and leg ultrasound examination), or alternative imaging techniques such as pulmonary angiography, MRI, or helical CT should be employed [38]. Similarly, if the chest radiograph reveals abnormalities that lead to difficulties in the diagnosis of PTE using ventilation–perfusion scanning, alternative imaging techniques are warranted. Helical CT scanning is likely to be of particular value. As the test becomes more widely available, it may threaten the role of ventilation–perfusion scans in the diagnosis of PTE. Helical CT can rapidly image the whole thorax within the time of a single breath hold with good visualization of the pulmonary arterial tree down to the level of the segmental arteries. Technical advances are likely to allow even greater resolution and faster image acquisition times. It may be useful to employ echocardiography of the right side of the heart, particularly when performed transesophageally, when PTE is suspected. This modality may allow direct visualization of thrombus in the pulmonary

arteries or right side of the heart. Indirect signs of PTE include a dilated hypokinetic right ventricle, tricuspid regurgitation, and high pulmonary artery pressures as measured with Doppler ultrasound. The radiation dose from investigations such as ventilation–perfusion scanning, chest radiography, helical CT, and even limited venography is modest [39] and is considered to pose a negligible risk to the fetus, particularly when set in the context of the risk from PTE. Objective diagnostic testing should not be withheld because of concern regarding fetal radiation exposure.

Assays for D-dimer are now used as a screening test for VTE in the nonpregnant patient, in whom they have a high negative predictive value [35]. A low level of D-dimer suggests the absence of VTE, and further objective tests are not performed. An increased level of D-dimer leads to an objective diagnostic test for VTE. In pregnancy, the level of D-dimer can be increased owing to the physiologic changes in the coagulation system, particularly if there is a concomitant problem such as pre-eclampsia or hemorrhage (conditions that are themselves risk factors for VTE). A positive D-dimer test in pregnancy is not necessarily consistent with VTE, and objective diagnostic testing is required. A low level of D-dimer in pregnancy and in the nonpregnant patient suggests that there is no VTE. Nonetheless, there is limited information on the efficacy and safety of D-dimer screening for VTE in pregnancy, and, until more information is available, firm guidance cannot be given.

The following thrombophilia screening performed at the time of presentation and before starting anticoagulant therapy can be useful in women with VTE:

- Activated partial thromboplastin time (may identify anticardiolipin antibodies)
- Prothrombin time (aids in interpretation of low protein C or S)
- Thrombin time (can identify problems such as dysfibrinogenemia or heparin contamination)
- Activated protein C resistance (genetic testing for factor V Leiden; only required when there is evidence of activated protein C resistance on the modified test for this resistance that predilutes the test sample with factor V deficient plasma)
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Prothrombin G20210A mutation
- Lupus anticoagulant
- Anticardiolipin antibodies (IgG and IgM)

This screening should include a family history of thrombosis. Although the results of a thrombophilia screen will not influence immediate management, they may influence the duration and intensity of anticoagulation, such as when antithrombin deficiency is identified. One must be aware of the effects of pregnancy and thrombus on the results of a thrombophilia screen. For example, protein S levels fall in normal pregnancy, making it extremely difficult to make a diagnosis of protein S deficiency. Activated protein C resistance occurs in approximately 40% of pregnancies, and anticardiolipin antibodies can influence the result of this test. Antithrombin may be reduced when thrombus is present. In liver disease, protein C and protein S will be reduced. Genotyping for the presence of factor V Leiden and prothrombin G20210A is not influenced by pregnancy or thrombosis. Thrombophilia screens must be interpreted by clinicians with specific expertise in the area. As noted previously, factor V Leiden is associated with an increase in the risk for VTE largely owing to DVT rather than PTE [40]. This observation may reflect a more adherent and stable thrombus with factor V Leiden, reducing the likelihood of embolization. Whether this effect applies in pregnancy is not yet established.

Antithrombotic therapy in pregnancy

Low molecular weight heparins are the anticoagulants of choice in pregnancy owing to the fetal hazards of coumarin [41] and side effects of unfractionated heparin. Warfarin is not secreted in breast milk in clinically significant amounts and is safe to use during lactation but crosses the placenta and is a teratogen. Warfarin embryopathy (midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short phalanges) can occur in approximately 4% to 5% [41] of fetuses exposed between 6 and 9 weeks' gestation. Substitution of heparin for warfarin during the first trimester can prevent this side effect. The risk of embryopathy may be dose dependent, with an increased risk when the dose of warfarin is greater than 5 mg/day [42]. In addition to warfarin embryopathy, there is the possibility of problems arising owing to fetal bleeding. Because the fetal liver is immature and levels of vitamin K–dependant coagulation factors low, maternal warfarin therapy maintained in the therapeutic range will be associated with excessive anticoagulation and potential bleeding problems in the fetus. Warfarin should be avoided beyond 36 weeks' gestation [41] because of the excessive bleeding risk

to the mother and fetus in the peripartum period. In addition, recent data suggest that prenatal exposure to coumarin is associated with an increased risk of disturbance in development manifest as minor neurologic dysfunction or a low intelligence quotient in school-aged children, with a relative risk of 7.6 for two or more of these minor abnormalities [43].

In contrast to warfarin, unfractionated heparin [44] and LMWH do not cross the placenta [45,46] as determined by measuring heparin activity in fetal blood, and there is no evidence of teratogenesis or risk of fetal hemorrhage. Based on a systematic review, these agents seem to be safe for the fetus [47]. Heparins are not secreted in breast milk and can be used during breast feeding. Prolonged use of unfractionated heparin can be associated with symptomatic osteoporosis (approximately 2% incidence of osteoporotic fractures), allergy, and heparin-induced thrombocytopenia [48]. LMWHs are associated with substantially less risk of osteoporosis. A recent study randomized women to receive unfractionated heparin or dalteparin for thromboprophylaxis in pregnancy and measured bone mineral density in the lumbar spine for up to 3 years after delivery [49]. Bone density did not differ in the healthy controls and dalteparin group but was significantly lower in the unfractionated heparin group when compared with the controls and dalteparin-treated women. Multiple logistic regression revealed that the type of heparin therapy was the only independent factor associated with reduced bone mass. Heparin-induced thrombocytopenia is a rare but life-threatening side effect. It is an idiosyncratic immune-mediated reaction associated with extensive VTE that usually occurs between 5 and 15 days after the institution of heparin. The risk has been estimated to be 1% to 3% with unfractionated heparin and is substantially lower with LMWH [50]. Allergic reactions usually take the form of itchy erythematous lesions at the injection sites. Switching heparin preparations may be helpful; however, a degree of cross-reactivity can still occur. Allergic reactions should be distinguished from faulty injection technique with associated bruising. Almost 1500 cases of prophylaxis or treatment of VTE in pregnancy with enoxaparin and dalteparin, the two most commonly reported LMWHs in pregnancy, have been reported in the literature. The risk for recurrent VTE has been approximately 1.2% and the risk for symptomatic osteoporotic fracture, 0.007% (Greer IA, 2002). LMWH is now the heparin of choice in pregnancy because of its better side-effect profile, good safety record for the mother and fetus, and once daily dosing [47,51–56].

Dextran should be avoided in pregnancy and alternative thromboprophylactic measures employed because of the risk for maternal anaphylactoid reactions, which have been associated with uterine hypertonus, profound fetal distress, and a high incidence of fetal death or profound neurologic damage [57].

Graduated elastic compression stockings are effective in the nonpregnant patient and, in view of the pregnancy-related changes in the venous system, could be of considerable value in pregnancy. They may act by preventing overdistension of veins, preventing endothelial damage and exposure of subendothelial collagen [58]. They also can be employed in acute DVT. Other mechanical techniques, such as intermittent pneumatic compression, are of value during cesarean section and immediately postpartum for prophylaxis.

Hirudin, a direct thrombin inhibitor used in the nonpregnant patient for the treatment of heparin-induced thrombocytopenia, is also used for postoperative prophylaxis. Because this agent crosses the placenta, it should not be used in pregnancy. It has been used in a lactating mother because of heparin-induced thrombocytopenia and was not detectable in breast milk [59].

Aspirin has been found in a meta-analysis to have a beneficial effect in the prevention of DVT. Its effectiveness in pregnancy in comparison with heparin remains to be established, but it is likely to offer some benefit. Its effectiveness is likely to be less than that of LMWH [60]. In women who are unable to take heparin, or in whom the balance of risk is not considered sufficient to merit heparin, aspirin may be useful in combination with compression stockings. Low-dose aspirin (60–75 mg daily) is not associated with an adverse pregnancy outcome in the second and third trimesters [61,62].

Management of acute venous thromboembolism in pregnancy

When DVT or PTE is suspected clinically, treatment with unfractionated heparin or LMWH should be given until the diagnosis is excluded by objective testing, unless anticoagulation is contraindicated. Thromboembolic deterrent stockings should be employed along with leg elevation for DVT. Analgesia for pleuritic pain and oxygen are often required in patients with PTE. Traditionally, unfractionated heparin has been used in the initial management of VTE when such treatment reduces the risk for further thromboembolism when compared with no treatment [63–66]. Failure to achieve the lower limit of the

target therapeutic range of the aPTT ratio is associated with a 10 to 15 fold increase in the risk for recurrent VTE [67]. Frequently, use of the aPTT to monitor unfractionated heparin is poorly performed and is technically problematic, particularly in late pregnancy when an apparent heparin resistance occurs owing to increased fibrinogen and factor VIII. This effect can lead to unnecessarily high doses of heparin with subsequent hemorrhagic problems. When such problems are considered to exist, it may be useful to determine the anti-Xa level as a measure of heparin dose (target range, 0.35–0.7 U/mL) [63]. Alternatively, LMWH could be employed. Two meta-analyses of randomized controlled trials have compared LMWH with unfractionated heparin in the initial treatment of DVT in nonpregnant subjects [68,69]. LMWH was found to be more effective than unfractionated heparin with lower mortality and was associated with a lower risk of hemorrhagic complications. LMWH has been as effective as unfractionated heparin in the initial treatment of PTE in studies carried out in nonpregnant subjects [70]. LMWH has been used for the initial management of VTE in pregnancy [53,71,72] and has been recommended for this purpose [24]. Occasionally, thrombolytic therapy may be required for life-threatening PTE or when a massive DVT threatens limb viability. Experience is limited, and there is a risk of major hemorrhage if systemic thrombolysis is used around the time of delivery or postpartum.

Unfractionated heparin can be given by continuous intravenous infusion or by subcutaneous injection. Unfractionated heparin is preferred to LMWH by some authorities in the initial management of massive PTE because of its rapid effect and the extensive experience in this situation. The dose is adjusted by monitoring the aPTT, with a therapeutic target ratio of 1.5 to 2.5 times the mean laboratory control value. The aPTT should be performed 6 hours after the loading dose and then on a daily basis. Protocols for heparin dose adjustment according to aPTT ratio results can be useful [63,73], and each laboratory should standardize its own target range for the aPTT ratio [63,72]. If anti-Xa measurements are used to monitor heparin, the target range is 0.35 to 0.70 IU/mL. Subcutaneous unfractionated heparin is an effective alternative to intravenous administration. In a meta-analysis of randomized controlled trials, 12 hourly subcutaneous unfractionated heparin was as effective and at least as safe as intravenous unfractionated heparin in the prevention of VTE in nonpregnant patients with acute DVT [74]. When administered subcutaneously, unfractionated heparin is given in subcutaneous injections of 15,000 to 20,000 IU, 12 hourly, after an initial intravenous bolus of 5000 IU. The dose should be adjusted to maintain the midinterval aPTT between 1.5 and 2.5 times the control [72].

In nonpregnant patients, once daily administration with LMWH is recommended for acute treatment of VTE (enoxaparin, 1.5 mg/kg body weight once daily; dalteparin, 10,000–18,000 U once daily depending on body weight). In view of the alterations in the pharmacokinetics of dalteparin and enoxaparin during pregnancy [75,76], the author recommends a twice daily dosage regimen for these LMWHs in the treatment of VTE in pregnancy (enoxaparin, 1 mg/kg twice daily; dalteparin, 100 U/kg twice daily up to a maximum of 18,000 U/24 hours). These doses are also used to treat VTE in the nonpregnant patient. The regimen for the administration of a LMWH (enoxaparin) in the immediate management of VTE in pregnancy is shown in Table 6 [72]. The initial dose of enoxaparin is 1 mg/kg twice daily, based on the early pregnancy weight, because LMWH does not cross the placenta. Enoxaparin is available in syringes of 40, 60, 80 100 and 120 mg. The dose closest to the patient's weight should be employed and should be continued 12 hourly until objective testing has been performed. If the diagnosis of VTE is confirmed, treatment is continued. Peak anti-Xa activity (3 hours postinjection) can be measured by a chromogenic substrate assay to confirm that an appropriate dose has been given. A suitable target therapeutic range is 0.6 to 1.2 U/mL. If the peak anti-Xa level is above the upper limit of the therapeutic target range, the dose of LMWH should be reduced and peak anti-Xa activity reassessed. The author's experience indicates that satisfactory anti-Xa levels are obtained using this regimen, and further monitoring of these levels can be deferred until the next routine working day [71]. Indeed, the experience suggests that this dose regimen rarely requires adjustment, and monitoring with assays for anti-Xa is probably unnecessary except at extremes of body weight. Care must be taken in women with a very high body mass index, in whom it is critical to ensure that an appropriate dose of heparin is used [1].

Table 6
Initial dose of enoxaparin for acute treatment of venous thromboembolism

Early pregnancy weight (kg)	Initial dose of enoxaparin
<50	40 mg twice daily
50–69	60 mg twice daily
70–89	80 mg twice daily
≥ 90	100 mg twice daily

With heparin therapy, the platelet count should be monitored 4 to 8 days after treatment commences, followed by testing on a monthly basis to detect heparin-induced thrombocytopenia. Pregnant women in whom heparin-induced thrombocytopenia develops and who require ongoing anticoagulant therapy should be managed with the heparinoid [77] danaparoid sodium.

Because coumarin is contraindicated in pregnancy, subcutaneous LMWH is usually used for maintenance treatment of VTE for the remainder of the pregnancy [71,78,79]. Women can be taught to self-inject and can be managed as outpatients once the acute event has been dealt with. Arrangements should be made to allow for safe disposal of needles and syringes. Evidence suggests that therapeutic doses of heparin should be employed for maintenance therapy, because a high recurrence rate of VTE was reported (47%) in a prospective randomized controlled trial in nonpregnant patients when thromboprophylactic doses of unfractionated heparin (5000 IU every 12 hours) were employed after initial management with intravenous unfractionated heparin [79]. The duration of therapeutic anticoagulant treatment in the nonpregnant situation is usually 6 months. Because pregnancy is associated with prothrombotic changes in the coagulation system and venous flow, it would seem logical to apply this duration of therapy to pregnancy. If the VTE occurs early in the pregnancy, and if there are no additional risk factors, the dose of LMWH could be reduced to prophylactic levels (40 mg of enoxaparin once per day or 5000 IU of dalteparin). Following delivery, treatment should continue for at least 6 weeks. Coumarin therapy can be used following delivery. If the woman chooses to use coumarin postpartum, it can usually be initiated on the second or third postnatal day. The international normalized ratio (INR) should be checked on day 2 and subsequent warfarin doses titrated to maintain the INR between 2.0 and 3.0 [80]. Heparin treatment should be continued until the INR is greater than 2.0 on 2 successive days.

Considerations for labor and delivery

The woman receiving anticoagulants should be advised that, once she is established in labor or thinks that she is in labor, she should not inject any further heparin until she has been assessed. Further doses should be prescribed by medical staff on an individualized basis. Generally, when the induction of labor is planned, the dose of heparin should be reduced to a thromboprophylactic level on the day before delivery. Graduated elastic compression stockings can be worn to provide some thromboprophylaxis. The treatment dose (twice daily administration) should be recommenced following delivery. Because of the small risk for epidural hematoma formation during spinal instrumentation in anticoagulated patients, epidural anesthesia should be sited only after a discussion with a senior anesthetist. There must be a degree of caution in the concomitant use of LMWH and neuraxial anesthesia, with vigilance for signs of cord compression. The combination must be avoided in patients undergoing therapeutic anticoagulation. In women receiving prophylactic doses of heparin and LMWH, neuraxial anesthesia should be avoided around the time of peak heparin levels. The timing of anesthesia and heparin administration need to be adjusted. Generally, regional techniques are not used until at least 12 hours after the previous prophylactic dose of LMWH. When a woman presents during a therapeutic regimen of LMWH (ie, twice daily regimen), regional techniques should not be employed for at least 24 hours after the last dose of LMWH. LMWH should not be given for at least 3 hours after the epidural catheter has been removed, and the cannula should not be removed within 10 to 12 hours of the most recent injection [81–83].

For elective cesarean section, the woman should receive a thromboprophylactic dose of LMWH on the day before delivery. On the day of delivery, the morning dose of LMWH should be omitted and the operation performed as soon as possible thereafter. Graduated elastic compression stockings can be worn or mechanical methods used to provide some thromboprophylaxis intraoperatively. A thromboprophylactic dose of LMWH should be given by 3 hours postoperatively and after removal of the epidural catheter. The treatment dose should be recommenced that evening. This practice reflects the general principles of management, and individualized management plans are often required with regard to anticoagulant treatment. There is an increased risk of wound hematoma following cesarean section with the use of unfractionated heparin and LMWH of approximately 2%. Consideration should be given to the use of drains (abdominal and rectus sheath) at cesarean section, and the skin incision should be closed with staples or interrupted sutures to allow for drainage of any hematoma that develops [84].

If there is a high risk for hemorrhage in a patient in whom continued heparin treatment is considered essential, she should be treated with intravenous unfractionated heparin until the risk factors for hemorrhage have resolved. Intravenous unfractionated heparin has a short duration of action, and

anticoagulation will reverse soon after cessation of the infusion should a hemorrhagic problem occur. Risk factors that should lead to the use of intravenous unfractionated heparin include recent major antepartum hemorrhage or coagulopathy, progressive wound hematoma, suspected intra-abdominal bleeding, and postpartum hemorrhage [84].

Thromboprophylaxis in pregnancy

In the woman with a previous VTE associated with a risk factor that is no longer present and with no additional risk factor or underlying thrombophilia, antenatal LMWH should not be prescribed routinely. This strategy must be discussed with the woman and her views taken into account, especially in view of the wide confidence intervals reported by Brill-Edwards et al (rate of recurrence, 0%; 95% CI, 0–8.0) [29]. Graduated elastic compression stockings with or without low-dose aspirin can be employed antenatally in these women. Postpartum, the patient should receive anticoagulant therapy for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily, or coumarin [target INR, 2–3] with LMWH overlap until the INR is $\geq$ 2.0) with or without wearing graduated elastic compression stockings (Table 7).

In women with a single previous VTE and an underlying thrombophilia, in women in whom the VTE was idiopathic, or in women who have additional risk factors such as obesity, there is a stronger argument for pharmacologic prophylaxis antenatally, although this regimen will depend in part on the severity of the previous event and the type of thrombophilia. Antenatally, these women should be considered for prophylactic doses of LMWH (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily) with or without wearing graduated elastic compression stockings. More intense LMWH prophylaxis in the presence of antithrombin deficiency is usually prescribed (eg, enoxaparin, 0.5–1 mg/kg 12 hourly, or dalteparin, 50–100 IU/kg 12 hourly) [85], although many women with previous VTE and antithrombin deficiency are maintained on long-term anticoagulant therapy. Postpartum anticoagulant prophylaxis for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily, or coumarin [target INR, 2–3] with LMWH overlap until the INR is $\geq$ 2.0) with or without wearing graduated elastic compression stockings is recommended.

For the woman with multiple previous VTE and no identifiable thrombophilia who is not receiving long-term anticoagulant therapy, there is a consensus that she should receive antenatal LMWH thromboprophylaxis and wear graduated elastic compression stockings. Postpartum, she should receive at least 6 weeks of pharmacologic prophylaxis with either LMWH or warfarin. If she is switched to coumarin postpartum, the target INR is 2 to 3, and LMWH should be continued until the INR is 2 or greater. A longer duration of postpartum prophylaxis may be required for women with additional risk factors.

The woman with previous episodes of VTE receiving long-term anticoagulants (eg, with underlying thrombophilia) should be switched from oral anticoagulants to LMWH by 6 weeks' gestation and be fitted with graduated elastic compression stockings. These women should be considered at very high risk for antenatal VTE and should receive anticoagulant prophylaxis throughout pregnancy. They should be advised, ideally pre-pregnancy, of the need to switch from warfarin to LMWH as soon as pregnancy is confirmed. The dose of LMWH given should be closer to that used for the treatment of VTE rather than that used for prophylaxis (eg, enoxaparin, 0.5–1 mg/kg 12 hourly, or dalteparin, 50–100 IU/kg 12 hourly. It should be noted that 12 hourly injections may be preferable to once daily injections in view of the increased clearance of LMWH in pregnancy]) based on the early pregnancy weight [85]. The platelet count should be checked before and 1 week after the introduction of LMWH, followed by monthly checks. Postpartum, the patient should resume long-term oral anticoagulants with LMWH overlap until the INR is in the pre-pregnancy therapeutic range and wear graduated elastic compression stockings.

In the woman who has a heritable thrombophilia diagnosed on laboratory testing, such as a woman with a positive family history, but who has no prior VTE, surveillance or prophylactic LMWH with or without graduated elastic compression stockings can be used antenatally. In antithrombin-deficient women, there is a strong argument for antenatal LMWH. Similarly, in a symptomatic kindred, antenatal LMWH is recommended. Postpartum, these women should receive anticoagulant therapy for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily, or coumarin [target INR, 2–3] with LMWH overlap until the INR is $\geq$ 2.0) with or without wearing graduated elastic compression stockings. These women usually require specialized and individualized advice from clinicians with expertise in the area.

Women undergoing cesarean section or vaginal delivery should undergo a risk assessment for VTE [52]. In the patient undergoing cesarean section, thromboprophylaxis (eg, 40 mg of enoxaparin or

Table 7
Suggested management strategies for prophylaxis in various clinical situations

Clinical situation	Suggested management
Single previous VTE associated with a temporary risk factor that is no longer present and no additional current risk factors such as obesity	Antenatal: Surveillance or prophylactic doses of LMWH are indicated (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily) ± graduated elastic compression stockings. Discuss decision regarding antenatal LMWH with the woman. Postpartum: Anticoagulant therapy is indicated for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily or coumarin [target INR, 2–3] with LMWH overlap until the INR is ≥2.0.) ± graduated elastic compression stockings.
Single previous idiopathic VTE or single previous VTE with underlying thrombophilia and not on long-term anticoagulant therapy, or single previous VTE and additional current risk factor(s) (eg, obesity, nephrotic syndrome)	Antenatal: Prophylactic doses of LMWH are indicated (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily) ± graduated elastic compression stockings. Note that there is strong support for more intense LMWH therapy in antithrombin deficiency (eg, enoxaparin, 0.5–1 mg/kg 12 hourly or dalteparin, 50–100 IU/kg 12 hourly). Postpartum: Anticoagulant therapy is indicated for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily or coumarin [target INR, 2–3] with LMWH overlap until the INR is ≥2.0.) ± graduated elastic compression stockings.
More than one previous episode of VTE, with no thrombophilia and not on long-term anticoagulant therapy	Antenatal: Prophylactic doses of LMWH are indicated (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily) + graduated elastic compression stockings. Postpartum: Anticoagulant therapy is indicated for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily or coumarin [target INR, 2–3] with LMWH overlap until the INR is ≥2.0.) + graduated elastic compression stockings.
Previous episode(s) of VTE in women receiving long-term anticoagulants (eg, with underlying thrombophilia)	Antenatal: A switch should be made from oral anticoagulants to LMWH therapy (eg, enoxaparin, 0.5–1 mg/kg 12 hourly or dalteparin, 50–100 IU/kg 12 hourly) by 6 weeks' gestation + graduated elastic compression stockings. Postpartum: Long-term oral anticoagulants should be resumed with LMWH overlap until the INR is in the pre-pregnancy therapeutic range + graduated elastic compression stockings.
Thrombophilia (confirmed laboratory abnormality) but no prior VTE	Antenatal: Surveillance or prophylactic LMWH is indicated ± graduated elastic compression stockings. The indication for pharmacologic prophylaxis in the antenatal period is stronger in AT-deficient women than in the other thrombophilias, in symptomatic kindreds when compared with asymptomatic kindreds, and also when additional risk factors are present. Postpartum: Anticoagulant therapy is indicated for at least 6 weeks (eg, 40 mg of enoxaparin or 5000 IU of dalteparin daily or coumarin [target INR, 2–3] with LMWH overlap until the INR is ≥2.0.) ± graduated elastic compression stockings.
Following cesarean section or vaginal delivery	Carry out risk assessment for VTE. If additional risk factors such as emergency section in labor, age over 35 years, or a high BMI present, consider LMWH thromboprophylaxis (eg, 40 mg of enoxaparin or 5000 IU of dalteparin) ± graduated elastic compression stockings.

Specialist advice for individualized management of patients is advisable in many of these situations.
Abbreviations: AT, antithrombin; BMI, body mass index; INR, international normalized ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

5000 IU of dalteparin) should be prescribed if she has one or more additional risk factors, such as emergency section in labor, age greater than 35 years, or a high body mass index. In patients at high risk, graduated elastic compression stockings should also be used. Stockings can also be employed if heparin is contraindicated. In the woman undergoing vaginal delivery, a similar strategy can be used, with LMWH prescribed if there are two or more additional risk factors [1] or one major risk factor such as morbid obesity.

Summary

Pulmonary thromboembolism is a major cause of maternal mortality. DVT causes significant morbidity in pregnancy and in later life owing to the post-thrombotic syndrome. Obstetricians must have an understanding of the risk factors for VTE, the appropriate use of prophylaxis, the need for objective diagnosis in women with suspected VTE, and the appropriate use of anticoagulant therapy. Greater use of prophylaxis is needed after vaginal delivery. Because acute VTE is relatively uncommon, greater use of proposed guidelines [24,84,85] may be of value in improving management, but the involvement of clinicians with expertise in the management of these cases is also important.

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