

Sex and gender issues and venous thromboembolism¹

Lisa Moores, MD^a, Kathryn L. Bilello, MD^b, Susan Murin, MD, MSc^{c,*}

^a*Critical Care Medicine, Department of Internal Medicine, Uniformed Services University of Health Sciences and Walter Reed Army Medical Center, 6900 Georgia Avenue Northwest, Washington, DC 20307-5001, USA*

^b*Division of Pulmonary and Critical Care Medicine, University of California, San Francisco–Fresno Program, and Central California Faculty Medical Group, 445 North Cedar, Fresno, CA 93702, USA*

^c*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of California–Davis School of Medicine, and Veterans Affairs Northern California Healthcare System, 4150 V Street, Suite 3400, Sacramento, CA 95817, USA*

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are generally considered to be different but related manifestations of a single disease process, venous thromboembolism (VTE). Based upon a number of epidemiologic studies of varying design, the current best estimate of the cumulative incidence of diagnosed or fatal VTE is 0.71 to 1.17 cases per 1000 adult population per year [1]. This figure, applied to the United States population, leads to the estimate of approximately 250,000 such cases annually. However, because underdiagnosis of VTE is common, some authorities believe that the actual total annual incidence, including undiagnosed, nonfatal cases, may be much higher.

The relationship between DVT and PE is clear. DVT of the lower extremities can be found in a majority of patients with PE, and approximately half of patients with DVT have evidence of PE, though PE is clinically silent in many of these cases. In most clinical studies of VTE, DVT is diagnosed approximately twice as often as PE, but in series including many autopsy-diagnosed cases, PE is diagnosed more

often than DVT [2,3]. This discrepancy is presumably due to a combination of underdiagnosis of PE during life and detection of clinically irrelevant pulmonary emboli at autopsy in patients dying of other causes.

Venous thromboembolism: epidemiology and risk factors

A wide variety of clinical conditions and circumstances are recognized as risk factors for VTE (Box 1). These include numerous medical disorders, such as malignancy and congestive heart failure, immobility from a variety of causes (the postoperative state, stroke, prolonged travel), and a variety of inherited and acquired conditions that cause a prothrombotic state (thrombophilia).

The clinical importance of a thrombophilic disorder depends on both the magnitude of thrombotic risk it conveys and the prevalence of the disorder. Deficiencies of the endogenous anticoagulants antithrombin (AT), protein C, and protein S are relatively uncommon. In the last decade, two highly prevalent forms of thrombophilia—Factor V Leiden and prothrombin 20210A variant—have been described. Some form of heritable thrombophilia can be identified now in more than one third of unselected patients with VTE and in the majority of patients with familial thrombosis [4]. Although each of these conditions increases the relative risk of thrombosis, the absolute risk among affected individuals may remain low, and many will never suffer a thrombotic event. Individuals

* Corresponding author. Division of Pulmonary and Critical Care Medicine, 4150 V Street, Suite 3400, Sacramento, CA 95817.

E-mail address: sxmurin@ucdavis.edu (S. Murin).

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Box 1. Risk factors for venous thromboembolism

Immobilization
 Age > 40
 Surgery within 3 months
 Stroke or paralysis
 Trauma/fracture
 Prior venous thromboembolism
 Malignancy
 Congestive heart failure
 Myocardial infarction
 Femoral venous catheter
 Diabetes mellitus
 Obesity
 Inflammatory bowel disease
 Race (African American > White > Hispanic > Asian)
 *Pregnancy and parturition
 *Oral contraceptive use
 *Hormone replacement therapy
 *Estrogen-antagonist therapy
 Thrombophilic conditions
 Factor V Leiden/resistance to activated protein C
 Prothrombin 20210A allele
 Protein C deficiency
 Protein S deficiency
 Antithrombin deficiency
 Dysfibrinogenemia
 Antiphospholipid antibodies (including lupus anticoagulants)
 Hyperviscosity syndromes
 Elevated levels of factors VII, IX, and XI
 Disorders of plasminogen and plasminogen activation

 * Risk factors specific to female gender

with the most profound thrombotic tendency often have multiple defects (such as homozygosity for Factor V Leiden or a combination of Factor V Leiden with another genetic abnormality).

Thrombophilia associated with the presence of antiphospholipid antibodies (APLAs) is the most common form of acquired thrombophilia. APLAs are a heterogeneous group of autoantibodies directed at phospholipids and protein-phospholipid complexes, and they include anti-cardiolipin antibodies and lupus anticoagulants. APLAs are risk factors for

arterial and venous thrombosis, other vascular disorders, and a variety of complications of pregnancy. In a nested case-control study within the Physicians Health Study, an anticardiolipin antibody above the 95th percentile was found to carry a fivefold relative risk of VTE [5]. However, a recent, prospective, population-based study found no association between anticardiolipin antibodies and VTE among healthy individuals with no evidence of autoimmune disease, suggesting the clinical import of such antibodies may vary in different populations of patients [6].

Both age and race affect incidence rates for VTE. VTE is very rare in childhood and uncommon among young adults. As shown in Fig. 1, the incidence of VTE rises dramatically after age 40 [2,7]. VTE incidence varies considerably by race. White et al [8] found an annual incidence of VTE of only six per 100,000 adult population for Asian-Pacific Islanders, compared with 14 per 100,000 for Hispanics, 23 per 100,000 among whites, and 29 per 100,000 among African Americans. Numerous other studies have confirmed different VTE incidence rates for different racial and ethnic groups. This is presumed to be largely due to differences in the prevalence of heritable risk factors for thrombosis between these groups, though other factors may also play a role.

A number of studies have examined the relationship between sex and the incidence of VTE. In the Worcester DVT Study, the incidence of VTE was no different for men and women [9]. A large epidemiologic study focusing on the elderly revealed a slightly higher rate of DVT but lower incidence rate of PE for women compared with men [10]. Male sex was associated with a slightly increased age-adjusted hazard ratio (1.4) in the Longitudinal Investigation of Thromboembolism Epidemiology (LITE) Study [11]. Similarly, a population-based study in Olmstead County, Minnesota found that men had a higher age-adjusted incidence rate than women, though this difference was small (overall male-female ratio 1.2:1), and the incidence of VTE was slightly higher among women than men before age 45 [2]. In the California Patient Discharge Data Set, the ratio of new cases of VTE among women to those among men was 1.2, overall. This was largely due to an increased incidence among very elderly women [8], but, as in the preceding study, incidence also was higher for younger adult women (those of childbearing age). A recent systematic review of published literature focusing specifically on DVT and, including several of the above-mentioned studies, found no systematic differences in incidence between the sexes [12]. Male to female incidence ratios varied from 0.8 to 1.3 in the seven, high-quality studies reporting sex as a variable.

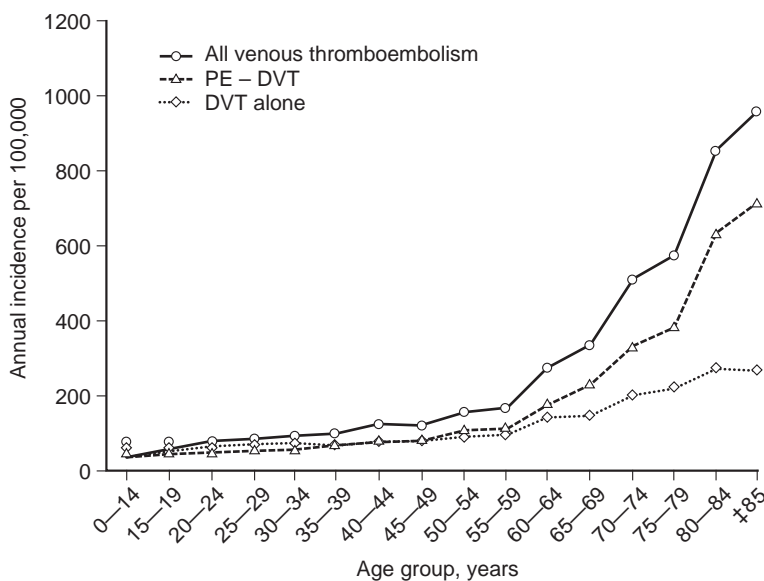


Fig. 1. Annual incidence of all venous thromboembolism, deep venous thrombosis alone, and pulmonary embolism with or without deep venous thrombosis among Olmstead County, Minnesota residents, 1966–1990, by age. (From Silverstein MD, Heit JA, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based, cohort study. *Arch Intern Med* 1998;158:585–93; with permission.)

Given the lack of consistency in the data on sex and VTE incidence, and the small differences observed in either direction, it appears that sex does not appreciably affect the overall incidence of VTE. However, gender is associated with a number of risk factors for VTE, as discussed later, and in some age groups these gender-specific risk factors may be associated with modest differences in the incidences of VTE between the two sexes.

The question of sex-related differences in the natural history of VTE has been less well studied. Data from the California Patient Discharge Dataset suggest minor differences in the patterns of recurrence of VTE for men and women [13]. A study assessing thrombus resolution by venography among patients with a prior DVT found that the male sex was associated with a greater degree of clot resolution [14]. Survival has been reported to be lower, and overall PE mortality higher among men than women in several studies [7,15], though this has not been a universal finding [16]. At this time the relationship between sex and the natural history of VTE has not been sufficiently well studied as to allow for any firm conclusions.

The main influence of gender upon VTE is through the relationship between gender and several clinical risk factors for VTE. The association between pregnancy and VTE is well established, and PE is one

of the leading causes of peripartum mortality. Increased risk of VTE is also associated with use of oral contraceptives (OCs), hormone replacement therapy, and estrogen-antagonist therapies. These exposures are unique (pregnancy and OCs) or nearly unique (estrogen agonist and antagonist therapies) to the female gender. The remainder of this article focuses on gender-specific risk factors for VTE among women, as well as upon special considerations in the diagnostic and therapeutic approaches to VTE in the pregnant patient.

Hormonal therapy and venous thromboembolism

Oral contraceptive medications

The evidence

OCs were first introduced in the late 1950s. The formulation of OCs has since changed considerably, with a progressive decrease in estrogen content and a change in the type of included progestin. Early OCs contained what are called first-generation progestins; formulations introduced in the 1970s contained second-generation progestins, and the third-generation medications were introduced in the early 1980s and 1990s. Most OCs used today are of the second- or third-generation type.

A possible association between OCs and VTE was first recognized in 1961 [17]. The existence and magnitude of an OC-mediated increase in VTE risk was a topic of intensive investigation and debate for years thereafter. Many early trials involved first-generation OCs no longer in use and are therefore less relevant to current practice [17–20].

Assessment of the relationship between OCs use and VTE has been complicated by both the difficulties inherent in studying rare events and the changes in OC formulations with time. There are no large, prospective, randomized trials examining the relationship between OCs and VTE as, given the low absolute rate of VTE in young women (estimated at 1 in 10,000) [17,19], such studies are not feasible. A randomized, controlled trial designed to look at cardiovascular outcomes in women using different OC formulations would need to enroll several hundred thousand women, and, with changes in drug formulations over time, prospective studies would have little impact on current practice when data collection and analysis were finally complete [21].

Most studies of OCs and the risk of VTE use case-control and retrospective cohort study designs. Douketis and colleagues [22] published a meta-analysis looking at all published studies through 1996. They reported pooled risk ratios of 3 for case-control studies, 4.8 for retrospective cohort studies, 2.4 for prospective cohort studies, and 1.1 for the single, randomized, controlled trial (of first-generation OCs). Although this analysis confirmed a probable association between OCs and VTE, the investigators cautioned that the reported risks from many studies are likely exaggerated given that the studies with the strongest methodology reported overall risk ratios < 3. In addition, several of these studies were conducted with older formulations and therefore might overestimate current risks [22].

Three of the largest studies included in this analysis have been frequently cited and deserve particular mention. The World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was a hospital-based, case-control study of more than 1000 women admitted for an episode of VTE. The overall risk of VTE in users of OCs was 3.5 times that of nonusers [20]. During the same year, investigators from the Boston Collaborative Drug Surveillance Program reported a case-control study that had used information from Britain's General Practice Research database. Crude estimates of the incidence of nonfatal VTE were four times higher in current versus past users of second-generation products [20]. The Transnational Research Group on Oral Contraceptives and the

Health of Young Women study, designed to look at the risk of VTE in users of the different generation products, also confirmed an overall fourfold elevated risk of VTE in current users of any OC formulation [20]. A recent, well-designed case-control study, not included in the meta-analysis by Douketis, of all women patients presenting with a VTE event in Denmark over the 5-year period (1994 through 1998) confirmed an increased risk up to sevenfold when comparing current users versus never users, with the highest risk occurring during the first year of use [23]. Given the consistencies in these data, it seems that the low absolute rate of VTE events in young women increases twofold to threefold among women using OCs [17,19,24] and that the relative risk of developing VTE is highest during the first 6 months of use, regardless of formulation used. Risk returns to baseline after use of these medications is discontinued.

Biologic explanation

OCs are believed to exert their effect on the risk of thrombosis by causing alterations in endogenous coagulation and fibrinolytic systems [17]. OC use is associated with increases in prothrombin, factors VII, VIII, and X, and fibrinogen levels and decreases in factor V levels. These effects may be more pronounced in users of third-generation pills [19,25]. Estrogens also cause a dose-dependent activation of the endogenous fibrinolytic system [26]. Changes in the levels of plasminogen, tissue plasminogen activator, and plasmin-plasminogen complexes among estrogen users have been described and indicate an overall increase in fibrinolytic activity, though other studies have shown conflicting results [19]. The balance of these changes seems to suggest that OCs induce an overall pro-coagulant effect [19,26]. However, all of these changes are small, the absolute numbers remain in the normal range, and thus the clinical significance is likely minimal.

More recent data suggest that OCs, and perhaps the progestin component in particular, may have profound effects on the anticoagulant system [26]. OCs induce an acquired resistance to the endogenous anticoagulant activated protein C (APC) [27]. In some users, the level of APC resistance associated with use of OCs approaches that seen in nonusers heterozygous for the factor V Leiden mutation, a heritable abnormality of the Factor V molecule that makes it resistant to APC's anticoagulant effect and is associated with a fivefold increase in the risk of VTE. Compared with second-generation pills, third-generation products cause a highly significant additional increase in APC resistance [28], and this has been postulated as the basis for the apparent increased

Box 2. Factors affecting oral contraceptive – associated venous thromboembolism risk

- Initial use
- Increasing age
- Estrogen dose
- Progestin type
- Smoking
- Obesity
- Health status
- Factor V Leiden mutation
- Other heritable thrombophilias

risk of VTE with third- as compared with second-generation pills [26]. Whether the phenomenon of acquired APC resistance that occurs in OC users is causal of VTE is unknown. OCs have been shown to have more pronounced effects on levels of clotting factors in women with prior OC-associated DVT, suggesting an interaction between environmental (OC use) and host factors [29].

Other risk factors

Exploration of the interaction between host and environmental factors has led to the identification of several other factors that are important in determining the actual risk of developing venous thrombosis. These factors are listed in Box 2 and then discussed.

Estrogen dose. Estrogen appears to have a dose-dependent effect upon VTE risk [17].

Progestin type. Most recent studies, and meta-analyses, confirm an approximately twofold to threefold increase in the risk of VTE in users of third- versus second-generation OCs [18–20,24,30–33].

Factor V Leiden and other heritable thrombophilias. Inherited disorders of coagulation are extremely important risk factors for the development of OC-associated VTE. The APC resistance conferred by the factor V Leiden mutation appears to be additive with that caused by OCs, resulting in a 20 to 30 fold increased risk of developing VTE compared with nonusers of OCs who lack the mutation. Patients with deficiencies of AT, protein S, and protein C deficiencies likely carry a sixfold to eightfold increased risk [17,34]. Although the prothrombin gene mutation appears to be a mild risk factor for thrombosis in most young people, it appears to play a greater role in combination with OCs, with a relative risk of 16 compared with noncarrier, nonusers [17].

Given the clearly increased risk of VTE among women with thrombophilia who use OCs, screening of all women for the most common of these disorders before prescribing OCs has been suggested. Given the low prevalence of AT, protein C, and protein S deficiencies in the population and the complexity of testing for these disorders, this is not practical. The high prevalence of the Factor V Leiden mutation in the general population, and the ease with which one can test for it, makes screening more feasible. Estimates of the number of patients this would involve and the associated costs vary widely, from \$5,000 to \$440,000 per prevented thrombus [35]. Others have argued that comprehensive screening would prevent only a very small number of fatal pulmonary emboli while potentially denying effective contraception to a large number of women [36]. Some have advocated careful personal and family histories to identify a subgroup of potential OC users for whom screening might have increased utility. However, two recent studies have shown that family history alone lacks sensitivity and would not improve the yield over general screening [37,38]. Although some gynecologic practices today likely do screen all of their women beginning OC treatment, at this time such an approach cannot be recommended and is not considered standard of care.

Other. Other factors found to increase the risk of VTE in OC users include advancing age, current tobacco use, increased body mass index, and overall poor health [17,18,23,24,39].

Summary

The use of OCs is associated with a twofold to threefold increase in the risk of developing VTE when compared with nonuse. Women who use third-generation drugs containing gestodene or desogestrel as the progestin component likely have a slightly greater risk than women using second-generation preparations. Obese patients and smokers are at increased risk. Women who appear to be at highest risk are those with an underlying inherited predisposition to thrombosis. Routine screening for heritable forms of thrombophilia before prescribing OCs is not currently recommended. Family history of VTE has not been shown to be a reliable variable in defining a subgroup of patients to screen. Occurrence of an episode of VTE while taking OCs should lead to cessation of therapy and no further use of these medications. If the event occurs in the setting of a known precipitant, such as recent surgery or immobilization, then the decision regarding further use of OCs should be individualized. At a minimum, the medications should be temporarily

discontinued with any further surgeries. Some authorities recommend that patients who develop idiopathic VTE while using OCs should be investigated for heritable thrombophilia, though it is not yet clear how this will affect therapy or if it should prompt family screening and there is no universal agreement on this point. Fortunately, the absolute risk of developing VTE while on OCs is low, allowing the majority of women to benefit safely from this convenient and effective form of contraception.

Hormone replacement therapy

The evidence

The term hormone replacement therapy (HRT) refers to a variety of estrogen or combined estrogen/progestin formulations prescribed to millions of women for proven benefits of menopausal symptom relief and osteoporosis prevention. Given the clear association between oral contraceptive use and VTE, and the similarities in the constituent hormones of HRT and OCs, concern for an increased risk of VTE among users of HRT was raised. Early studies on this topic were equivocal. In 1997, Douketis and colleagues [22] reviewed the existing literature and concluded that an association might exist but that further data were needed.

Studies published since 1996 have more consistently found an increased risk of VTE in women who use HRT. Between 1996 and the beginning of 2002, four prospective, randomized trials were published. The first three were not designed to look at VTE as a primary outcome, but tracked these episodes as adverse events. The Heart and Estrogen/Progestin Replacement Study (HERS) [40] was a randomized trial of the effect of HRT as a secondary prevention in women with heart disease. DVT and PE, recorded as secondary outcomes, occurred in 2.5% of the treatment group, as opposed to 0.9% of the placebo group, for a hazard ratio of 2.89 (95% CI 1.50 to 5.58). The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial [41] randomized healthy postmenopausal women to four different combinations of HRT as compared with placebo. Ten VTE events occurred in the estrogen treatment groups, and none occurred in the placebo group—a difference that did not reach statistical significance. The Estrogen Replacement and Atherosclerosis (ERA) trial [42] randomly assigned more than 300 women with proven coronary artery disease to estrogen, a combined estrogen/progestin, or placebo. VTE, again reported as an adverse event, was not significantly different among the groups. A meta-analysis that included these three trials, as well as eight case-controlled and one cohort

study, concluded that current estrogen use was associated with an increased risk of VTE (RR 2.14, 95% CI 1.64 to 2.81) [43]. This review also confirmed that the risk, as with OCs, is greatest in the first year of use [43]. The fourth study was designed to look for VTE as the primary outcome event. The Estrogen in VTE Trial (EVTET) [44] randomized 140 women with a prior history of VTE to a combination estrogen/progestin or placebo. The trial was terminated early because of new publications suggesting an increased risk of VTE in current users of HRT and a nonsignificant clustering of study endpoints at one of the centers (ie, the incidence of VTE in the HRT group was 10.7% compared with 2.3% in the placebo group). Although this did not reach statistical significance, it strongly suggested that women with a prior DVT have a high risk of recurrence if using HRT.

In 2002, Hulley and colleagues [45] reported follow-up data from the HERS study. The HERS II reported on noncardiovascular events occurring during the original 4 years of the randomized trial and an additional 3 years of open label follow-up. Over the 7-year period, the intention to treat hazard ratio (HR) for all venous thromboembolic events was 2.08 (95% CI 1.28 to 3.40). When adjusted for actual adherence to medication, the HR increased to 3.04 (95% CI 1.46 to 6.31). The risk of VTE was greatest early in use. The relative risk of any venous thromboembolic event during HERS was 2.66 (95% CI 1.41 to 5.04) as compared with 1.40 (95% CI 0.64 to 3.05) during HERS II.

The strongest evidence of an increased risk of VTE during HRT comes from the initial report of the Women's Health Initiative Trial published in July of 2002 [46]. This prospective, double-blinded, randomized controlled trial examined the major health benefits and risks of HRT in more than 16,000 postmenopausal women. The study was terminated early because interim analysis suggested the harms of HRT exceeded benefits. HRT users experienced a twofold greater rate of both DVT and PE, as well as all VTE. There was a decreasing risk of VTE with time. Although few women with prior VTE were enrolled, these women were found to be at an increased risk of recurrent events associated with HRT (HR 4.90, 95% CI 0.58 to 41.06 as compared with a HR of 2.06, 95% CI 1.54 to 2.76 in those without a prior history). No interaction between HRT and age, race, body mass index, smoking status, or aspirin use was seen [46].

Biologic explanation

The effects of HRT on the coagulation system appear to be similar to those of OCs with evidence for increased markers of coagulation, factor VII lev-

els, and APC resistance and a decrease in antithrombin levels [24]. Investigators in the EVTET trial looked at hemostatic variables during treatment with HRT and placebo [47]. There were no differences between the groups at baseline, but after initiation of HRT there was a highly significant decrease in the concentrations of all clotting inhibitors except free protein S, a decrease in Factor VIIa, and an increase in prothrombin fragments and D-dimer levels that was not seen in the placebo group. These changes were more pronounced in the women who eventually developed recurrent VTE, suggesting that some women are “high responders” in terms of estrogen’s effects on coagulation [47].

Although acquired resistance to APC is considered an important mechanism of clot formation in OC users, studies of APC resistance and HRT have not been conclusive, and further study is necessary to clarify the relationship among HRT, APC resistance, and VTE [48–51]. A summary of HRT effects on the hemostatic system can be found in [Box 3](#).

Other preparations

Dose-related increases in thrombogenic activity related to oral estrogens may be related to the first-

pass metabolism in the liver [52], which could be avoided by parenteral or transdermal administration. A number of studies have shown that transdermal HRT does not have the same adverse effects on the coagulation cascade as oral HRT. The effect of transdermal HRT on the risk of VTE is not clear, as no prospective studies have directly compared oral and transdermal formulations. A recent rigorous case-control study of 155 postmenopausal women with their first episode of idiopathic VTE found an odds ratio in current users of oral and transdermal HRT of 3.5 (95% CI 1.8 to 6.8) and 0.9 (95% CI 0.5 to 1.6), respectively, when compared with nonusers [53].

Other risk factors

The higher risk of VTE in early in the course of HRT suggests that, as with OCs, there may be a subgroup of women with underlying genetic disorders or acquired factors that put them at a particularly high risk. Women with underlying thrombophilias have an increased risk of VTE while using HRT, and these factors likely act synergistically [24,54]. The effect of other factors, such as age and smoking, on HRT-associated VTE risk is unknown, but the Women’s Health Initiative Trial suggests that any potential effect is minimal.

Use of HRT, like OC use, is associated with a two-fold increase in the risk of VTE. The absolute increase is low. Risk is highest in the first year of use and in women with underlying thrombophilias or prior history of VTE. Given the known benefits of HRT for relief of postmenopausal symptoms and prevention of osteoporosis, decision making about HRT should be individualized after careful weighing of risks and benefits. Use of transdermal formulations may not be associated with an increased risk of VTE, but further studies are needed. HRT use in women who have a prior history of VTE is not recommended.

Other hormones

Selective estrogen receptor modulators

Two selective estrogen receptor modulators (SERMs) are currently used with some frequency. Tamoxifen is used primarily for the prevention and adjuvant treatment of breast cancer, and raloxifene has been approved for the prevention of osteoporosis and investigated in breast cancer prevention. Although these agents have anti-estrogenic properties, they also have partial agonist effects at selected receptors and might be expected to have some of the same side effects and associated risks as other estrogens.

The Breast Cancer Prevention Trial [55] reported a threefold increased risk of PE and a nonsignificant

Box 3. Effect of hormone replacement therapy on selected hemostatic markers

Increased

- Plasminogen
- Tissue plasminogen activator
- Plasmin-antiplasmin complex
- Thrombin-antithrombin
- D-Dimer
- Fibrin split products
- C-reactive protein

Decreased

- Factor VII
- Antithrombin
- Protein S
- Protein C

No proven Effect

- Resistance to activated protein C (though balance suggest a possible increase)
- Fibrinogen
- Factor X

Results vary among the studies, but the balance of the data suggests the effects listed above.

increased risk of DVT among women with breast cancer receiving tamoxifen. Other studies have not confirmed a significantly increased risk, though VTE was a secondary event and event numbers were low [56,57]. A large case-control study found a sevenfold increased risk of VTE when adjusted for obesity, smoking, and hysterectomy status [58], though the number of events was low. A large, randomized trial of raloxifene for breast cancer prevention found a relative risk for PE and DVT of 3.1 (95% CI 1.5 to 6.2) [59]. Preliminary studies suggest that, as with other hormonal agents, the SERMs likely induce changes in circulating clotting inhibitors, and the effect is likely more pronounced in women with underlying thrombophilias [60,61].

Summary

All forms of hormonal therapy commonly used by women today appear to be associated with increased risk of VTE. The risk is highest in the first 6 to 12 months of therapy. Certain subgroups of women are at particularly high risk, such as those with underlying thrombophilias, a prior history of VTE, and those who are older, obese, or currently use tobacco. These risks must be kept in mind and balanced with the potential benefits when prescribing any of these medications.

Pregnancy and venous thromboembolism

Pregnancy is a well-recognized risk factor for thromboembolic disease. It is estimated that pregnancy confers a threefold to fivefold increase in VTE risk compared with the nonpregnant state [62,63]. PE is a significant cause of maternal death in the industrialized world. In the United States Centers for Disease Control and Prevention's (CDC) Pregnancy-Related Mortality Surveillance Program, thromboembolism accounted for 11% of total pregnancy-related mortality [64], and it was the most common cause of maternal mortality in a recent review of maternal deaths in the United Kingdom [65].

Physiologic changes that occur during pregnancy pose several risks for the development of VTE. Hypercoagulability results from increased levels of fibrinogen and several clotting factors (II, VII, VIII, IX, X, XII) as well as decreased levels of inhibitors of coagulation such as protein S [66–68]. Acquired activated protein C resistance [69] and reduced fibrinolysis [70] have both been described in normal pregnancy. This altered state of coagulation persists throughout pregnancy and for up to 6 weeks post partum. Venous stasis occurs from hormonally in-

duced increases in venous distensibility and capacity as well as vena caval compression by the enlarging gravid uterus [71–73]. Vascular injury resulting from childbirth, and especially delivery by caesarean section, further escalates risks for VTE during the peripartum period; caesarian section is associated with a further increase in the incidence of VTE compared with vaginal delivery [74]. Other risk factors for VTE during pregnancy include obesity, maternal age, parity, prolonged bed rest, infection, prior history of VTE, and thrombophilia [75].

Clinical presentation and diagnosis of venous thromboembolism in the pregnant patient

The clinical presentation and diagnostic evaluation of suspected VTE do not differ substantially for the pregnant and nonpregnant patient. Although comprehensive discussion of the manifestations and evaluation of VTE is beyond the scope of this article, issues uniquely relevant to VTE in pregnancy are discussed later. For a discussion of issues common to the pregnant and nonpregnant patient, see several recent reviews [72,73,76–78].

The typical signs and symptoms of VTE, leg swelling and pain, dyspnea, and chest pain, are common during pregnancy and are usually caused by processes other than VTE. Not surprisingly, the prevalence of VTE in clinically suspected cases is significantly lower in pregnant women when compared with the nonpregnant population. For example, in the nonpregnant population, one in four patients with suspected DVT will prove to have DVT [79] and one in four patients with suspected PE will prove to have PE [80]. In contrast, in a study of pregnant women presenting with clinically suspected DVT, the diagnosis was confirmed in < 10% of cases [81]. Likewise, the prevalence of PE was < 5% in a study of 120 consecutive pregnant women presenting with suspected PE [82].

DVT appears to occur more frequently in the antepartum period and disproportionately affects the left leg (approximately 90% cases, compared with 55% of cases in nonpregnant patients) possibly due to compression of the left iliac vein by the right iliac artery as they cross [83]. PE is diagnosed more commonly in the postpartum period, especially after cesarean delivery [84].

The evaluation of patients with suspected VTE involves assessment of pretest clinical suspicion of VTE followed by objective confirmation with diagnostic tests. Diagnosis of VTE in pregnancy is problematic because of concerns about the performance of tests that expose the fetus to radiation, as well as by

the paucity of studies offering evidence-based guidelines to direct the diagnostic work up of VTE during pregnancy. Consequently, the clinician often is left to extrapolate a diagnostic approach from studies performed in the nonpregnant population.

Ionizing radiation carries risks of both teratogenicity and oncogenicity, and fetal risks of radiologic procedures used in the evaluation of VTE have been examined [85]. Cumulative radiation dose absorbed by the fetus in the work-up of VTE falls below 5 rad, a level that has not been associated with a significant risk of fetal injury in most studies [85]. In fact, the combination of chest radiograph, ventilation-perfusion lung scan, and pulmonary angiogram on average exposes the fetus to < 0.5 rad. The risk of childhood cancer after in utero radiation exposure is increased slightly; however, the absolute incidence of cancer in the first 10 years of life remains low at approximately 0.2% [86]. In a recent review of pregnancy outcomes of 120 women who underwent ventilation-perfusion (V/Q) scanning during pregnancy, there was no increase in adverse pregnancy events. In follow up of more than 90% of offspring after a mean age of 120 months, there was no increase in malignancies or developmental abnormalities [82]. Magnetic resonance imaging (MRI) during pregnancy has been less well studied. MRI appears to be safe to the fetus in the short-term, but long-term risk is unknown [87].

Diagnosis of suspected DVT during pregnancy should begin with compression ultrasonography (CUS). A negative ultrasound result coupled with low clinical suspicion probably requires no further evaluation, although some experts recommend serial CUS (over subsequent 7 days) to exclude propagation of calf vein thrombosis [72]. If clinical suspicion of deep venous thrombosis is high, then further diagnostic work up is required. Options would include definitive diagnosis with venography or magnetic resonance venography (MRV) versus serial CUS (with treatment withheld for serial negative CUS). Although withholding anticoagulation in the setting of serially negative impedance plethysmography (IPG) was shown to be safe in 139 pregnant patients with suspected DVT and initial negative IPGs [81], this study has not been validated with CUS. Isolated iliac vein thrombosis is suggested by back pain with swelling of the entire leg and requires MRV or venography for diagnosis as CUS is insensitive for the diagnosis of iliac vein thrombosis [72,73,88].

Recent clinical studies (in nonpregnant patients) have demonstrated the value of adding D-dimer measurement to other tests in diagnostic algorithms designed to minimize invasive testing for both DVT and PE [89–91]. The merit of D-dimer testing rests

with its high negative predictive value (up to 97% as a stand-alone test). D-dimer levels increase as pregnancy progresses as well as in complicated pregnancies, which may limit their usefulness as a diagnostic tool in this population. To date there are no management studies incorporating D-dimer measurement into the clinical work-up of pregnant patients with suspected VTE.

After initial assessment and chest radiography, V/Q scanning is generally the recommended initial test in the evaluation of suspected PE. However, because DVT and PE are closely related disorders and their management usually identical, some experts recommend CUS (which avoids fetal radiation exposure) as the initial test in the evaluation of suspected PE during pregnancy [73]. Patients with CUS indicative of DVT are treated, and negative CUS are followed by further testing.

V/Q scanning has long been the cornerstone of the diagnostic approach to the patient with suspected PE. Chan and associates [82] published a recent retrospective review of V/Q scan findings and outcome in 120 consecutive pregnant women with suspected PE referred for lung scanning. The distribution of scan patterns was markedly different from that reported in the nonpregnant population. Of the 113 scans performed in women who were not on anticoagulation before testing, 73.5% were interpreted as normal, 24.8% as nondiagnostic, and 1.8% as high probability. In contrast, in the nonpregnant population, normal scans are found in 27% to 36% of patients, nondiagnostic scans in 47% to 59% of patients, and high probability scans in 8% to 14% of patients [80,92]. The high percentage of normal scans probably reflects the relative youth of the pregnant population, with fewer comorbid lung conditions present to cause abnormal perfusion scans. The lower percentage of high probability scans likely reflects the lower prevalence of PE in pregnant patients presenting with clinical suspicion of PE. One hundred four cases (80 with normal scans and 24 with nondiagnostic scans) were not anticoagulated, and no VTE events were reported over a mean 20.6 months of follow-up. The investigators concluded that a normal lung scan safely excludes VTE, as is the case among nonpregnant patients.

Patients with nondiagnostic V/Q scans (neither normal nor high probability) require further evaluation according to the clinician's pretest suspicion of PE. In the setting of low pretest probability, serial CUS is suggested. Moderate or high pretest probability dictates a more definitive approach, and pulmonary angiography, considered the "gold standard" diagnostic test for PE, should be considered in such cases.

Helical CT has become a popular form of diagnostic imaging for PE, and replacement of both V/Q scans or pulmonary angiography by CT in management algorithms for suspected PE has been suggested [93]. However, this remains a hotly debated issue, with some experts believing the test is not yet sufficiently sensitive [94,95]. Many management studies incorporating helical CT in the diagnostic management of PE have not included pregnant patients [96,97]. A recent study calculated the average fetal radiation dose with helical CT using a PE protocol to be less than that with V/Q scanning [98]. Although the current role of helical CT in the diagnostic approach to the pregnant patient with suspected PE remains unclear, it is likely that helical CT will play a major role in the future, as imaging technology improves and further experience is gained with such imaging in this population.

Treatment of venous thromboembolism during pregnancy

Anticoagulation during pregnancy must consider fetal as well as maternal safety. Unfractionated heparin (UFH), low molecular weight heparin (LMWH), and the heparinoid danaparoid sodium do not cross the placenta and therefore do not cause fetal bleeding or birth defects, although bleeding at the uteroplacental junction can occur [99]. The safe use of UFH and LMWH during pregnancy has been well established [100,101]. In contrast, coumarin derivatives do cross the placenta and can cause an embryopathy as well as fetal hemorrhage [99]. For these reasons, coumarins should be avoided during pregnancy. Although efficacy has been demonstrated for adjusted dose UFH (given subcutaneously every 12 hours in doses adjusted to achieve a therapeutic activated partial thromboplastin time), LMWH is favored by most experts as the anticoagulant of choice during pregnancy [72], though the substantial cost of the medication may be a deterrent in some practice settings. Advantages of LMWH include fixed weight-based dosing without need for monitoring APTT, lower incidence of heparin-induced thrombocytopenia, and lower incidence of heparin-induced osteoporosis [99]. Given the long duration of anticoagulant treatment (until at least 6 weeks after delivery), development of osteoporosis is a justifiable concern. Dahlman [102] noted a 2.2% incidence of vertebral fracture in a study of 184 women receiving prophylactic dose UFH during pregnancy. The dose of LMWH dose must be adjusted as the pregnancy advances and weight is gained. This may be done by changing the dose according to the increased weight or by performing weekly anti-factor Xa levels and targeting dose to a level of approxi-

mately 0.5 to 1.2 U/mL [99]. Treatment of VTE should last at least 3 to 6 months. If the event occurred early in pregnancy, after conclusion of treatment VTE prophylaxis with LMWH or UFH should be maintained until at least 6 weeks postpartum. LMWH should be discontinued 24 hours before elective induction of labor to minimize risk of bleeding during delivery. If spontaneous labor occurs in a woman taking LMWH, protamine may be administered if bleeding risk seems significant. However, clinical series have not shown significant bleeding complications with LMWH [103]. To minimize risk of epidural hematoma, epidural and spinal anesthesia should be delayed at least 12 hours after a prophylactic dose of LMWH and 24 hours after a therapeutic dose of LMWH [104]. After delivery, warfarin may be substituted for heparin. Neither warfarin nor the heparins are secreted in breast milk.

Thrombophilia and pregnancy-related venous thromboembolism

Thrombophilia is an important additional risk factor for thrombosis during pregnancy. Some form of hereditary or acquired thrombophilia contributes to more than half of all maternal thromboembolic events [75,105]. In addition to maternal thromboembolism, thrombophilia is associated with increased prevalence of multiple adverse pregnancy outcomes—miscarriage, intrauterine growth restriction, preeclampsia, abruption and intrauterine death [75,106]—that are thought to result from thrombosis of the uteroplacental circulation [107]. Several case-control and cohort studies have linked thrombotic complications of pregnancy to multiple thrombophilic disorders including factor V Leiden and prothrombin G20210A mutations, protein C and protein S deficiencies, antithrombin deficiency, hyperhomocysteinemia, and antiphospholipid antibody syndrome [5,108–118]. Early studies of VTE incidence in pregnant and postpartum women with thrombophilia demonstrated a high frequency of thromboembolic events, ranging from 47% in postpartum antithrombin deficient women to 14% in postpartum women with protein S deficiency [114]. However, these studies of women who had already suffered a thrombotic event were flawed by selection bias. Friederich and colleagues [114] partially circumvented this obstacle by determining the frequency of VTE during pregnancy among asymptomatic female family members of patients with a history of VTE and known deficiency of antithrombin, protein C, or protein S. The risk for VTE was increased eightfold in factor-deficient women compared with nondeficient women in this

cohort; however, the absolute risk of VTE was only 4.1% (7 of 169 pregnancies), a much lower frequency than that previously reported. It likely still overestimates risk, given that the study population was drawn from symptomatic kindred who have higher event rates than individuals without a family history of thrombosis. In a case-control study of 119 women with pregnancy-related VTE, Gerhardt and associates [115] evaluated the prevalence of inherited thrombophilia. The odds ratio for VTE was 9.3 for women with factor V Leiden and 15.2 for women with the G20210A prothrombin-gene mutation. The presence of combined factor V Leiden and G20210A prothrombin-gene mutation conveyed a markedly higher risk as reflected by an odds ratio of 107. In a similarly designed study of 119 women with a first episode of VTE during pregnancy or the puerperium [112], the odds ratio for VTE was 9.1 among women with any thrombophilia, 10.6 for carriers of factor V Leiden, 2.9 for carriers of the G20210A prothrombin gene mutation, and 13.1 for antithrombin, protein C, or protein S deficiency (considered as a group). Although relative risks are increased, absolute risks for pregnancy-related thrombosis are, for most forms of thrombophilia, low; AT deficiency, particularly the quantitative (Type I) deficiency, is the exception. Absolute risks have been calculated at approximately 1 in 500 for Factor V Leiden, 1 in 200 for prothrombin 20210A, 1 in 100 for protein C deficiency, and 1 in 2.8 and 1 in 42 for quantitative and qualitative forms of antithrombin, respectively [115,119]. Whereas most investigations of the pregnancy-related risks associated with APLAs have focused on the well-recognized association with pregnancy loss, increased risk of intra or postpartum thromboembolism is another complication associated with such antibodies [116,120].

General screening of pregnant women for thrombophilia is not supported by the literature, and it cannot be recommended. However, screening should be considered for pregnant women with a personal or family history of VTE as well as those women with pregnancy complications, such as recurrent miscarriage, intrauterine growth restriction, severe preeclampsia, placental abruption, and intrauterine fetal death that suggest an increased likelihood of thrombophilia [99].

Management of pregnant women with thrombophilia or history of prior venous thromboembolism

Women with a known thrombophilic condition or a prior history of VTE have an increased risk of pregnancy-related VTE. Given the effectiveness of prophylactic anticoagulant therapy in reducing the

incidence of VTE, appropriate selection of women who will benefit from prophylaxis is important. Decisions regarding VTE prophylaxis during pregnancy are complex and must take into account all factors that collectively influence the individual's risk for VTE. Idiopathic VTE or VTE associated with a permanent clinical risk factor is associated with a higher rate of recurrence than VTE associated with transient risk factors, such as prior surgery [121]. The type of thrombophilia also affects the risk of thrombosis. AT deficiency, homozygosity for factor V Leiden or prothrombin gene mutations, combinations of different thrombophilias, and APLA syndrome are all associated with greater thrombogenic potential than the lesser thrombophilias. Finally, other individual risk factors, such as morbid obesity, and situational risk factors, such as the need for prolonged bed rest, must be considered.

Estimates of risk for thromboembolism during pregnancy among women with a history of VTE vary significantly, from 0% to 13% [99]. A recently published study by Brill-Edwards and associates [122] added significantly to our knowledge about recurrence risk and thus management, of pregnant women with a history of prior VTE. One hundred twenty-five pregnant women with a single previous episode of VTE were prospectively evaluated for antepartum VTE recurrence. Women with known thrombophilia or VTE within 3 months of study enrollment were excluded. Antithrombotic treatment was withheld in all patients until 24 hours after delivery at which time treatment with UFH and warfarin was started, with anticoagulation continued for 4 to 6 weeks postpartum. Ninety-five of the women were screened for thrombophilia after completion of the trial. Only 3 of 125 women (2.4%) had an antepartum recurrence of VTE. None of the 44 women without thrombophilia and whose previous thrombosis was associated with a temporary risk factor had a recurrence. In contrast, 3 of 51 women (5.9%) with thrombophilia or a previous episode of idiopathic thrombosis, or both, had a recurrence. These findings show that the risk of antepartum VTE among women with a prior history of VTE is low and suggests that women without thrombophilia or prior idiopathic VTE do not require prophylaxis during the antepartum period. However, postpartum treatment with warfarin is recommended based on higher risk for PE and the absence of fetal risk during this period.

It remains unanswered whether women with asymptomatic thrombophilia or a single prior idiopathic thrombotic event require antepartum prophylaxis. Guidelines for management of pregnant patients at increased risk for VTE have been published

Table 1

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.

(From Greer IA. Prevention and management of venous thromboembolism in pregnancy. Clin Chest Med 2003;24:123–7; with permission.)

[99,123] and offer considerable flexibility in the approach to prophylaxis during the pregnancy. Postpartum anticoagulation is recommended for 6 weeks in nearly all women with prior VTE or known thrombophilia. The most recent recommendations are summarized in Table 1. Women with a history of multiple (more than two) episodes of VTE or women receiving long-term anticoagulation for prior VTE should be treated with UFH (adjusted dose) or LMWH (prophylactic or adjusted dose) during pregnancy with resumption of long-term anticoagulation postpartum [99].

Summary

Pregnancy poses several risks for the development of VTE. Although the prevalence of VTE is low in pregnant women presenting with clinically suspected VTE, aggressive pursuit of a definitive diagnosis is essential to avoid the potentially fatal complication of PE, a common cause of maternal death. Diagnosis will necessarily incorporate algorithms and technologies untested in the pregnant population, so that application of sound clinical judgment is essential. Studies highlighting the increased risk of both VTE and adverse outcomes of pregnancy in women with thrombophilia have multiplied, enhancing our understanding of the relation between thrombophilia and thrombotic risk during pregnancy. Evidence-based guidelines, such as those published by the Sixth ACCP Consensus Conference on Antithrombotic Therapy, are presently our best resource for managing thrombotic complications of pregnancy.

Summary

At least 250,000 episodes of VTE leading to hospitalization or death are estimated to occur in the United States each year. A number of clinical and demographic risk factors for VTE are recognized, with the latter including both age and race. Overall, the incidence of VTE does not appear to vary significantly by sex, as evidenced by a lack of consistency in the magnitude and even direction of effect of sex in a variety of epidemiologic studies of varying design. Several studies have shown a higher incidence among women than men during childbearing age. The issue of a gender effect on the natural history of VTE has not been well studied. The main influence of gender on VTE is the relationship between female gender and several well-recognized clinical risk factors for VTE: oral contraceptive use, hormone replacement therapy, estrogen receptor modulator therapy, and pregnancy.

Hormonal therapies are associated with a twofold to threefold increase in VTE incidence. Risk is higher with some formulations than others, during initial use, and among women who are obese, smoke, or have one of several forms of heritable thrombophilia. The pregnant state is associated with a threefold to fivefold increase in VTE risk, and thromboembolism is a major cause of peripartum death. Heritable thrombophilias are also important co-determinants of VTE risk in pregnancy. The mechanisms through which pregnancy and hormonal therapies increase VTE risk have not been definitively established, but hormonal effects on levels of coagulation and anticoagulation factors likely play a role. Venous compression and venous injury also contribute to increased risk during pregnancy and the puerperium.

Approaches to diagnosis of VTE in the pregnant woman are largely the same as in the nonpregnant patient, but special treatment considerations do apply. Warfarin is embryopathic, particularly between the 6th and 12th weeks of pregnancy, and should be avoided in favor of heparin or low-molecular weight heparin when treatment of the pregnant woman is necessary. Guidelines have been published to assist the clinician in decision making about prophylaxis of pregnant women at increased risk or pregnancy-related or post-partum VTE.

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