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Venous thromboembolism in women

Suman Rathbun

Abstract: The risk of venous thromboembolism (VTE) varies throughout a woman's life and is associated primarily with underlying hormonal exposure. Alteration in hemostatic mechanisms, including resistance to activated protein C, may explain this altered risk. Initially, development of VTE with the use of contraception in young adulthood may reveal inherited thrombophilia. Pregnancy, and particularly the post-partum period, likely confer the greatest risk of VTE, but the absolute risk is small. Guidelines for prevention of VTE during pregnancy are based on personal or family history of VTE, and known inherited thrombophilia. Use of hormone replacement therapy later in life is associated with increased risk of VTE, and may be safest if given as an estrogen-only preparation to young postmenopausal women for less than 5 years. Universal screening for thrombophilia prior to pregnancy or initiating hormonal therapy is not recommended; however, selected testing in high-risk groups may be warranted. The lack of firm recommendations for the prevention of VTE in women highlights the need for future investigation aimed at identifying high-risk groups and evaluating the efficacy of prophylactic measures.

Key words: contraception; hormone replacement therapy; pregnancy; venous thrombosis; women

Epidemiology of venous thromboembolism in women

Venous thromboembolism (VTE) risk varies throughout a woman's life, with hormonal exposure likely underlying this risk. This varying risk may be dependent on both the dose and duration of estrogen exposure including use of contraceptive therapy, pregnancy and hormone replacement therapy (HRT). In addition, the risk of VTE in women is influenced by innate factors of age, race, weight, and thrombophilia, as well as external factors such as the formulation, dose and duration of estrogen and progestin administration. Venous thromboembolism should be carefully considered as an important women's health issue.

Most studies report the overall risk of VTE as similar in women compared with men, but there are specific trends related to sex. In a multi-center, cross-sectional, observational study performed on more than 1,500 general surgical patients in Italy, more women than men had risk factors for VTE, most commonly varicose veins, obesity and estrogen therapy.[1] Eighty percent of women and 67% of men had at least one risk factor, and 51% of women and 35% of men had at least two risk factors. Simon and colleagues in a recent retrospective case–control study reported that lifetime estrogen exposure may be related to the overall risk of VTE.[2] After statistical adjustment for other common risk factors for VTE, it was found that the risk of VTE increased by 6% for each year's delay in menopause. Moreover, women with higher parity, especially those with more than two children, were at higher risk. The combination of late menopause and oral estrogen use had the highest risk of VTE. Other studies have confirmed an association of late menopause and increased parity with risk of VTE.[3,4]

A 3-year European study of patients with first episode VTE reported the risk of recurrent VTE was four times greater in men compared with women.[5] This risk prediction has been further refined by other studies demonstrating that women with first VTE secondary to hormone therapy, specifically oral contraceptive pills (OCPs), are at much lower risk for VTE recurrence compared with men or women who suffered a non-hormone treatment-related event.[6] In this study, the increased risk of recurrent VTE in men was more modest (1.2 to 3 times increased risk). Other studies have found no increased recurrence risk in men compared with women.[7,8] The etiology of this potential association

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is not clear. Confounding due to older age, homocysteinemia, and site of thrombosis has been excluded.[9]

Venous thromboembolism and contraception

Methods of contraception have been evolving since the introduction of oral contraceptives in the early 1960s. It was recognized early that high doses of estrogen of more than 100 micrograms led to increased cardiovascular risk. Reduction of the estrogen dose with the addition of a progestin component led to reduced cardiovascular risk and improved cycle control, but with androgenic adverse effects. Subsequently, more selective, less androgenic progestins were developed, but these were found to have less effectiveness in preventing pregnancy.[10] Recently, the FDA has questioned the effectiveness of these newer, lower dose preparations in preventing pregnancy compared with older preparations of the 1970s, and has convened a panel of experts to investigate whether the improved safety profile outweighs a slightly increased risk of unwanted pregnancy.

Over the past 10 years, studies have attempted to quantify the risk of VTE associated with the use of different contraceptive preparations. This risk is influenced by various factors including the presence of thrombophilia, age, weight, estrogen dose, progestin dose and preparation, and route of administration. Overall, with use of OCPs, the risk of VTE is increased two- to eightfold in users compared with non-users,[11–16] translating into an absolute annual risk of 0.48% in women without thrombophilia and 4.6% in those with hereditary protein C, S or antithrombin deficiency.[17] This elevation in risk must be put into context with the very low absolute risk of VTE with OCP use. For example, women of fertile age have a risk of VTE of one per 10,000 persons per year which increases to two to eight per 10,000 person-years with the use of OCPs compared with the social and economic consequences of pregnancy.[18,19]

The mechanism of increased thrombosis formation with hormonal contraception has revealed prothrombotic effects caused by elevated levels of prothrombin; Factors VII, VIII, IX, X, and XI; and fibrinogen with decreased levels of protein S and antithrombin. However, levels of antithrombotic proteins are also altered, including elevated levels of protein C, alpha-antitrypsin, and plasminogen with reduced levels of plasminogen activating inhibitor-1.[20,21] Resistance to activated protein C seems to underlie the major effect of OCPs' thrombogenic potential.[21] In a cross-sectional study of 180 healthy women, it was found that this activated protein resistance may be more pronounced with use of the newer third-generation OCPs compared with second-generation OCPs that contain levonorgestrel, and less pronounced in those using progestin-only OCPs.[22] Women receiving the fourth-generation cyproterone-containing OCPs, not currently FDA-approved in the USA, demonstrated the greatest resistance to activated protein C.[22]

Investigation of the temporal relationship between OCP use and VTE has revealed that risk is increased in first-time users of OCPs. This risk is especially elevated during the first 6 months of use, and likely reveals those who may have inherited clotting tendencies.[12,23–25] The risk returns to that of non-users within 1–3 months after discontinuation. Duration of use or lifetime cumulative exposure does not seem to affect VTE risk associated with OCP use, nor does re-exposure after a period of non-use.[11,25,26]

Few studies have documented the magnitude of interaction between age and OCP use. It is known that the incidence of VTE is rare before puberty, and increases with age.[27] The risk in women using OCPs over the age of 40 may be more than three times greater than in those less than 25 years of age.[25] Similarly, while it is well known that smoking increases the risk of cardiovascular events in women who use OCPs,[28] the risk of VTE in OCP users who smoke has been found to be increased approximately twofold.[11,12,29] It is generally recommended that women over 35 years old who smoke should not use OCPs. The evaluation of elevated body mass index (BMI) in conjunction with OCP use has shown that the risk of VTE is increased five- to tenfold, and is significantly elevated with a BMI greater than 30 kg/m^2.[11,12,29,30] This risk is multiplicative in the presence of smoking[12] (see Table 1).

The early recognition of increased cardiovascular disease with the use of OCPs prompted evaluation of the formulation of OCPs, scrutinizing both the dose of estrogen used as well as the formulation of the progestin component. Subsequently, the initial form of estrogen was changed from mestranol to ethinyl estradiol, and the estrogen dose was lowered from 150 micrograms (first-generation) to 50 micrograms or less (second-generation), with most preparations containing 30–35 micrograms in conjunction with a progestin. This reduction was effective in lowering the risk of cardiovascular disease, including the risk of VTE.[23,31–35] Owing to androgenic side effects of acne, hirsutism, weight gain, and altered lipid and carbohydrate metabolism, the progestin component was also reviewed, and studies were performed to evaluate any differences in risk with levonorgestrel found in second-generation OCPs compared with desogestrel or gestodene found in the newer third-generation formulations. Early studies showed that the risk of venous throm-

Table 1 Hormonal methods of contraception and risk of venous thromboembolism

Contraceptive	Risk of venous thromboembolism[a]
First-generation	
mestranol	+++
Second-generation	
ethinyl estradiol (EE) + progestin: norethindrone, levonorgestrel, norgestrel, ethynodiol diacetate	++
Third-generation	
EE + desogestrel or gestodene	+++
Fourth-generation	
EE + drospirenone, norgestimate	+++
Injectible	
medroxyprogesterone	+
Implantable	
etonogestrel	+
Transdermal	
EE + norelgestromin	++
Intrauterine	
levonorgestrel	+ (?)
Vaginal ring	
EE + etonogestrel	+ (?)

[a]Relative risk (lowest +, moderate ++, highest +++) compared with non-users.
?, uncertain; additional studies required.
Adapted from references 10 and 51.

bosis associated with third-generation OCPs was twofold higher compared with second-generation OCPs.[11,12,23,34] While these estimates were disputed as confounded by age,[35] two recent meta-analyses confirmed the increased risk of VTE with third-generation OCPs.[25,36] Newer fourth-generation preparations containing cyproterone acetate are also being evaluated, and preliminary studies reveal a fourfold increased risk in VTE compared with second-generation OCPs.[33,37] To date, no studies have been published that confirm the increased risk of VTE with the fourth-generation progestin drospirenone. In addition, there have been no apparent differences in incidence of VTE found between monophasic OCPs that provide a constant daily dose of estrogen and progestin compared to multiphasic OCPs that provide varying doses of the components throughout the cycle.[25]

The newest concept in OCPs is extended-cycle contraception to decrease the number of menstrual periods per year. In 2003, the FDA approved a monophasic regimen of ethinyl estradiol 30 micrograms and levonorgestrel 0.15 milligrams (Seasonale) to be given continuously for 84 days with 7 free days to produce menstruation.[10] In May 2006, a similar product was approved (Seasonique) but with 10 micrograms of ethinyl estradiol taken during the 7 menstrual days. In May 2007, a low-dose continuous OCP containing ethinyl estradiol and levonorgestrel (Lybrel) was approved to obviate menstrual periods altogether. To date, reports of VTE risk associated with these extended preparations indicate similar safety to more traditional OCPs.[38]

The transdermal contraceptive patch (Ortho Evra) containing a combination of ethinyl estradiol (20 micrograms) and the progestin norelgestromin (150 micrograms) was marketed in 2002. Since then, only one study has been published that evaluated the risk of VTE.[39] This case–control study compared the risk of non-fatal VTE in women receiving the transdermal contraceptive patch with monophasic or triphasic OCPs containing norgestimate and 35 micrograms of ethinyl estradiol. Overall, the risk of non-fatal VTE was no higher in those receiving the transdermal patch, although the effect of duration of use could not be evaluated. However, in November 2005, the FDA updated labeling of this product to alert clinicians that the product was associated with higher area-under-the-curve levels of ethinyl estradiol compared with other OCPs. Whether this increased exposure to estrogen translates into an increased risk of thrombosis is unknown.[40]

Preparations containing injectable (Depo-subQ provera), implantable (Implanon) or intrauterine (Merena, Nuvaring) progestins are infrequently used in the USA. Studies of the progestin etonogestrel in healthy volunteers have found small changes in the levels of protein C, protein S, prothrombin, and antithrombin, but little effect on activated protein C resistance.[41] Other investigations have found similar results with injectible levonorgestrel.[42] Clinically, most case–control studies are small but have revealed a minimal effect of progesterone-only preparations on the risk of VTE when used for contraception; however, the risk may be greater depending on the specific progestin used; for example, greater with 19-nortestosterone derivatives.[25,43,44] These preparations carry less risk of VTE compared with combination estrogen/progestin products, and may be an option for women at high risk for VTE. Currently, the package inserts of progesterone-only preparations disclose that usage may increase the risk of VTE, but this warning is not displayed on the product label.

Finally, recent approval of post-coital contraception (morning after pill) has raised questions about its safety given the higher doses of estrogen and progesterone contained in the preparation. In a population-based cohort study, use of post-coital contraception did not result in any episodes of VTE, and likely does not confer a higher risk compared with traditional OCPs.[45]

The interaction between thrombophilia and contraceptive use has been extensively evaluated for the heterozygous Factor V Leiden and prothrombin G20210 mutations. First estimates of a

multiplicative association were derived from the Leiden Thrombophilia Study[46] which revealed a 37-fold increased risk of VTE in individuals with heterozygous Factor V Leiden mutation using OCPs compared with non-carrier, non-OCP users. Absolute risk could be estimated as an annual incidence of VTE of 28.5 per 10,000 women-years. Other studies have shown increased risk but with lower estimates.[47,48] Homozygous Factor V Leiden mutation likely carries greater risk.[49–51] Combined mutations of Factor V Leiden and prothrombin may elevate risk 16-fold.[18,47,49,50] The risk with genetic thrombophilia is highest during the first 6 months of use and declines thereafter.[24] Activated protein C resistance in the absence of Factor V Leiden mutation also has been associated with an increased risk of VTE, but not as significant as in carriers of the mutation.[52] While it is known that third-generation OCPs confer greater VTE risk compared with second-generation preparations, whether this is multiplicative in the presence of thrombophilia is unknown.[31,47,51,53]

Other inherited thrombophilias including protein C, S, and antithrombin deficiency have been found to confer increased VTE risk in the magnitude of two- to sixfold compared with non-OCP users.[14,54] Elevated levels of Factor VIII have been found to be associated with a fourfold increase in VTE risk in OCP users.[55] Re-analysis of the Leiden Thrombophilia Study also revealed associations between elevated levels of Factor II and Factor XI and increased risk of VTE in OCP users.[56]

Risk of VTE at other sites, including cerebral vein thrombosis, portal vein thrombosis and superficial thrombophlebitis with OCP use, has been reported. Studies report a 34-fold increased risk of cerebral vein thrombosis in carriers of both Factor V Leiden mutation and protein G mutation.[57–60] Genetic thrombophilia has been found to be a risk factor for portal vein thrombosis, but OCP use was not associated.[61] Remote studies reported an association between OCP use and superficial thrombophlebitis; however, recent reports have refuted this risk.[62,63]

Venous thromboembolism during pregnancy

The reported risk of venous thromboembolism during pregnancy is estimated at 18 per 100,000 women during pregnancy to 1900 per 100,000 women post-partum,[64] with one recent study reporting the risk as 1.72 per 1000 deliveries.[65] Overall, the risk of VTE is five times more likely in pregnant women. Pulmonary embolism remains the most common cause of pregnancy-related maternal death in developed countries,[66] with a case fatality rate of 2.4%.[65] Pregnancy is associated with changes in the normal hemostatic equilibrium. Concentrations of fibrinogen may increase up to threefold, accompanied by increases in Factors VII, VIII, IX, X, XII, and von Willebrand factor with the highest levels seen at term.[67] While levels of prothrombin and Factor V are relatively unchanged during pregnancy, Factors XI and XIII decline. In addition, there is acquired resistance to activated protein C, and a reduction in protein S. Venous stasis and hormone-related increases in venous capacitance also predispose to VTE during pregnancy.

Only recently has longitudinal data been presented that describes the risk throughout pregnancy.[64,65] These studies demonstrate a relatively constant rate of VTE during the last 20 weeks of pregnancy, with at least half of VTE occurring during the post-partum period. The incidence of VTE increases with age, especially over the age of 35, but younger women aged 15–19 had the highest risk overall in one study.[64] The reasons for this finding are not clear and have not been reproduced. The risk is found to be greater in black women compared to women of other ethnic backgrounds.[65,68] Smoking is associated with a higher risk of VTE during pregnancy. Also significant, are obesity, lupus, pre-existing heart disease, sickle cell disease and pre-eclampsia, and births requiring transfusion.[65,69] While there are few studies, caesarian section may increase the risk twofold compared with vaginal birth.[65,70] One surveillance study of 15 women undergoing C-section revealed 46% of patients had asymptomatic pelvic vein thrombosis detected by pelvic vein magnetic resonance venography.[71] Further, VTE has been found to be a major contributor to the higher rate of post-partum death associated with C-section compared with vaginal birth.[72]

A history of VTE or known thrombophilia is consistently associated with higher risk. There has been interest in the risk of VTE with hyperemesis gravidarum. An investigation of 16 women admitted with hyperemesis compared to matched controls revealed significant coagulation activation during pregnancy.[73] Clinically, one study revealed a two- to threefold increased risk of VTE in women with hyperemesis.[65] Additionally, there are reports of large vein thrombosis in patients undergoing in vitro fertilization complicated by ovarian hyperstimulation syndrome.[74]

Since the presence of thrombophilia may affect up to 20% of the population of European descent, the risk of thrombophilia-associated VTE during pregnancy has been evaluated in large case–control and cohort series.[75] One recent meta-analysis found a fourfold increased risk in patients with heterozygous Factor V Leiden mutation based on cohort studies alone that increased to eightfold if case–control studies were included.[76] Another meta-analysis reviewed the available data regarding the risk of VTE with

inherited thrombophilia and found that heterozygous and homozygous Factor V Leiden conferred a 34-fold and eightfold increase respectively in pregnancy-associated VTE compared with non-pregnant women, although the absolute risk remained low. Heterozygous prothrombin gene mutation was associated with a sevenfold elevation in risk. Antithrombin, protein C, and protein S deficiencies carried about a three- to fourfold increase in VTE risk. Homozygous methylenetetrahydrofolate reductase (MTHFR) mutation that is associated with homocysteinemia was not found to confer significant risk. The highest risk for VTE during pregnancy is in women with antiphospholipid antibodies commonly manifested as pregnancy loss after 10 weeks gestation.[77] Lupus anticoagulant antibodies confer higher risk than anticardiolipin antibodies.[77] One small study has reported a higher risk of VTE with type A or AB blood groups compared with women with the O blood type.[78]

The safe and accurate diagnosis of VTE during pregnancy represents an important challenge since few diagnostic tests have been specifically validated in pregnant women. One recent systematic review[79] evaluated the diagnostic utility and safety of tests for DVT and pulmonary embolism. Overall, only four studies met the predefined inclusion criteria. The investigators recommended that proximal lower extremity deep-vein thrombosis could be safely excluded using compression ultrasound in combination with a negative sensitive D-dimer, or based on two serial normal compression ultrasound examinations in patients with abnormal D-dimer levels. An abnormal compression ultrasound alone confirmed DVT in these patients. Further, the authors recommended that those with abnormal flow in the common femoral vein necessitated evaluation of the iliac veins by duplex or magnetic resonance venography. D-dimer, either used alone or in combination with pre-test clinical probability assessment, has not been validated as an effective sole exclusionary test during pregnancy. For diagnosis of pulmonary embolism, the authors recommended the use of either a nuclear perfusion scan or helical computed tomography (CT) scan, noting that the CT may be advantageous due to low fetal radiation exposure, fewer non-diagnostic tests, and the ability to show alternate diagnosis.[79] However, due to the paucity of studies evaluating diagnostic testing for VTE in pregnant patients, further investigation is needed.

VTE and hormone replacement therapy (HRT)

Most agree that HRT improves the symptoms of menopause, including hot flashes, depression, and sleep disturbance, and increases bone density; however, the cardiovascular benefit of HRT is disputed. These benefits must be balanced against the well-established increased risk of stroke, breast cancer and venous thromboembolism. Subsequently, the efficacy and safety of HRT have been the topic of rigorous meta-analyses, and large randomized controlled trials. Most oral preparations contain conjugated estrogens derived from pregnant mare urine or micronized estradiol and are given in combination with progesterone acetate to negate the increased risk of endometrial cancer in those with an intact uterus. Other preparations available include esterified estrogen, a synthetic estrogen derived from yams and soybeans. In addition, phytoestrogens have recently been marketed as a natural source of estrogen replacement.

Recent large prospective trials including the Heart and Estrogen/progestin Replacement Study (HERS) have found a two- to fourfold increase in VTE risk with HRT.[3] In the Women's Health Initiative, a randomized controlled trial of 16,608 postmenopausal women aged 50–79 years, a twofold risk of VTE with combination hormonal therapy was confirmed.[80] The risk is greater with a larger dose of estrogen administered (>1.25 mg/day),[81,82] and seems to be greater within the first year – returning to baseline within months of discontinuation of HRT.[82–87]

There is emerging evidence that the timing of HRT after menopause may influence the overall risk profile. In the Danish Osteoporosis Prevention Study (DOPS), a study of 2016 healthy postmenopausal women receiving HRT, investigators found no increased risk of VTE on 10-year follow-up in women aged 45–58 years.[88] These results could not be confirmed by re-analysis of the larger HERS and Women's Health Initiative trials since women were significantly older with too few younger women enrolled to confirm this possible reduced risk in younger women.

Women who have undergone hysterectomy are candidates for estrogen-only HRT. Review of studies reporting estrogen-only HRT reveal a modest increase of VTE risk of 1.3-fold, but there is large variability in study design with small numbers of patients enrolled.[89] Data from the Women's Health Initiative study in a group of 10,739 women aged 50–79 years without a uterus indicates the risk of VTE in women receiving estrogen-only HRT is increased during the first 2 years of use (hazard ratio 1.32), but is still less than that with a progestin combination.[90] A large case–control study in Washington State found that women using esterified estrogens had a lower risk of venous thrombosis compared with those using conjugated equine estrogens.[91] This lower risk may be explained by a

study finding less activated protein C resistance with esterified estrogen use.[92]

With the well-documented increase in VTE risk with oral HRT, the risk associated with transdermal HRT has been investigated. Transdermal administration bypasses the first-pass effect by the liver that may be responsible for induction of a pro-clotting state. Results of studies evaluating this risk have conflicted. Small studies initially indicated increased VTE risk with transdermal HRT, but more recent larger studies including the ESTHER study, a multicenter case–control study of VTE among postmenopausal women aged 45–70, showed no elevation in risk.[93–95] Further, the study results suggested that preparations containing norpregnane derivatives were more thrombogenic than those containing micronized progesterone or pregnane derivatives.[96]

There have been no controlled studies regarding the risk of VTE with nutritional supplements containing plant chemicals that have estrogen-like properties known as phytoestrogens: soy-based proteins containing the isoflavones genistein and daidzein. Although they may have some benefit in relieving the postmenopausal symptoms of hot flashes, the risks associated with their use are unknown.[97,98]

The risk of VTE associated with the use of the selective estrogen receptor modulators tamoxifen and raloxifene used in the treatment of breast cancer and osteoporosis is uncertain. Physiological studies have demonstrated reduced levels of antithrombin and protein S with little effect on protein C or activated protein C. These effects on hemostasis have translated into a twofold increase in risk found in some studies.[99] In a study of 10,000 women randomized to raloxifene or placebo for prevention of coronary heart disease or breast cancer, a 1.44-fold increased risk of VTE was seen.[100]

There are few studies evaluating the risk of HRT in women with a previous history of VTE. One small study found a fivefold increased risk of recurrent VTE in women who used HRT compared with non-users.[101] This finding was also seen in the Women's Health Initiative trial, but the number of women with a history of VTE was too small to reach significance.[80]

There are several case–control studies that document the increased risk of HRT use in women with genetic thrombophilia. The most widely studied is the interaction with Factor V Leiden mutation where the risk is up to 25-fold higher in those with the genetic mutation who used oral HRT compared with non-carrier, non-users.[18,89,90,102] A less significant elevated risk of VTE in those with the prothrombin mutation and oral HRT has been shown.[80,89,90] Women with Factor V Leiden or prothrombin gene mutation who receive either estrogen-only or transdermal estrogen HRT may not have additional risk of VTE above those who carry these mutations and do not use HRT.[89,90] Studies to date show no additional increased risk with oral HRT in patients with other risk factors including hyperhomocysteinemia, antiphospholipid antibodies or elevated Factor XI.[103,104] However, in one study, levels of Factor VIII correlated with risk of VTE in both estrogen/progestin and estrogen-only HRT users.[104]

Guidelines for screening of thrombophilia in women

The decision to screen for thrombophilia prior to initiation of OCPs or HRT or whether to use routine pharmacological prophylaxis in women with thrombophilia remains controversial. To date, no study has definitively shown the cost-effectiveness of screening for thrombophilia prior to institution of hormone therapy or pregnancy. A recent incremental cost-effectiveness analysis was conducted in the United Kingdom that found that universal screening for thrombophilia prior to prescription of hormone therapy was not cost-effective. However, the study suggested that selective testing in high-risk groups such as those with a history of VTE was a more economic strategy.[105] The strategy of identifying women at high risk for VTE by history, and selectively testing them for thrombophilia, seems to be the best approach, but has not been validated in prospective studies.[106] Combined hormonal contraception using estrogen-progestin is discouraged in women with known thrombophilia; however, progestin-only preparations may be relatively safe due to the lower risk of VTE.[51] Similarly, there is no guideline recommending thrombophilia testing prior to pregnancy in women without a history of VTE, but screening may be useful in those with recurrent pregnancy loss, a strong family history of VTE, or an individual history of VTE.

Prevention of VTE

No trial has assessed the benefit of pharmacological primary prevention of VTE in women using OCPs, including those with known thrombophilia.[15] Currently, there are no recommendations for discontinuation of OCPs prior to elective surgery. Appropriate prophylactic measures should be taken according to those recommended routinely for surgical procedures.

The recommendations for prevention of VTE during pregnancy originate from consensus panel review. The use of medical prevention with unfractionated heparin (UFH) or low-molecular weight

heparin (LMWH) in women with a history of VTE or known thrombophilia is controversial since there are no large randomized trials, and recommendations are based on small studies.[107] Two studies have evaluated the risk of recurrent thrombosis during pregnancy in women with a history of VTE and found it to be between 2% and 6% in women not receiving any pharmacological prophylaxis.[108,109] Women with known hereditary thrombophilia were at higher risk for recurrent VTE. Another study has found a recurrence rate of 15.5% in women with a pregnancy-related first VTE with similar incidence in those with known thrombophilia.[110] The consensus panel of the American College of Chest Physicians and others[111–114] give the following recommendations for prevention of VTE during pregnancy:

1) close observation or pharmacological prophylaxis in women with no prior VTE but known thrombophilia with the addition of post-partum anticoagulation
2) close observation without pharmacological prophylaxis in women with a history of VTE associated with a non-estrogen risk factor with initiation of prophylaxis for 6 weeks post-partum
3) close observation or prophylactic UFH or LMWH for women with a single idiopathic VTE followed by post-partum anticoagulation
4) use of prophylaxis with UFH or LMWH for women with a single VTE and known thrombophilia or strong family history
5) therapeutic dose UFH or LMWH in women with a history of recurrent VTE or on long-term anticoagulation
6) prophylactic dose LMWH for women with recurrent pregnancy loss due to thrombophilia
7) a combination of heparin and low-dose aspirin for women with known antiphospholipid antibodies and one or more fetal losses.

All women with a history of VTE should wear graduated compression stockings during pregnancy and the post-partum period (Table 2).

Fondaparinux has been used successfully during pregnancy in those who cannot tolerate other LMWHs.[115] The use of intermittent pneumatic compression devices during and after C-section has been found to be cost-effective,[116] and the use of prophylactic LMWH in women at moderate to high risk of VTE post C-section is under investigation.[117]

The treatment of acute VTE during pregnancy with either UFH or LMWH is safe and effective during pregnancy.[118] Either intravenous UFH or adjusted-dose LMWH for 5 days followed by adjusted-dose UFH or LMWH for the remainder of pregnancy is recommended.[113] More frequent dosing may be required since LMWH may be renally cleared more quickly in pregnancy, but there are no consistent guidelines regarding monitoring of anti-Factor Xa levels.[113,119] Major bleeding is rare and occurs with similar incidence to that in non-pregnant women. Heparin-induced thrombocytopenia and osteoporosis may occur after prolonged UFH use, but are much less common with LMWH use.[113,118] Anticoagulation should be discontinued 24 hours prior to elective induction of labor.[106] Use of thrombolytic therapy in pregnant women with life-threatening VTE has been reported.[120] For pregnant women with contraindications to anticoagulation, there is anecdotal evidence that the use of retrievable inferior vena cava filters is safe.[70] Heparin and LMWH do not cross the placenta and are not secreted into breast milk. Warfarin use has also been found to be safe for nursing mothers and their infants, and may be substituted post-partum and continued for at least 6 weeks.[121]

Prevention of VTE in those considering HRT should be aimed at avoidance in high-risk groups, including those with a history of VTE. In women with genetic thrombophilia who use HRT, the risk of VTE is elevated compared with non-users; however, the overall incidence remains low. Use of estrogen-only or transdermal estrogen confers less risk of VTE.[90] If required, low-dose estrogen HRT in younger women for a short duration for relief of postmenopausal symptoms is associated with the lowest risk of VTE. To date, studies have found no

Table 2 Recommended prophylaxis of VTE during pregnancy

Risk group	Recommendation
No VTE/thrombophilia	Surveillance + graded compression stockings[a]
History of single VTE/no thrombophilia	Surveillance + graded compression stockings or LMWH or UFH prophylaxis + 6 weeks pp
History of single VTE/thrombophilia	LMWH or UFH prophylaxis + 6 weeks pp
History of multiple VTE	LMWH or UFH treatment + warfarin pp
Recurrent pregnancy loss/thrombophilia	LMWH or UFH prophylaxis
Antiphospholipid antibodies	LMWH or UFH + low dose aspirin

[a]Graded compression stockings are recommended as prevention for all groups.
VTE, venous thromboembolism; LMWH, low-molecular weight heparin; UFH, unfractionated heparin; pp, post-partum.

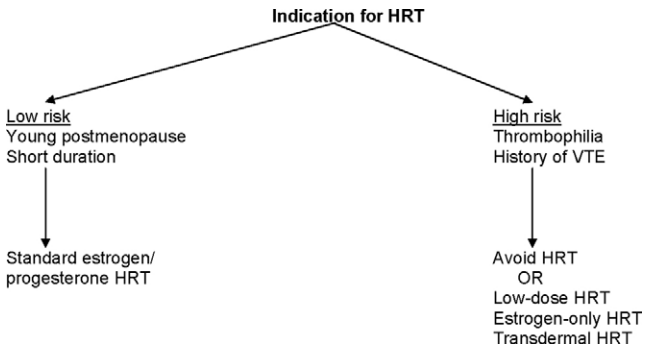

Figure 1 Assessment of venous thromboembolism (VTE) risk in patients desiring hormone replacement therapy (HRT).

increase in postoperative VTE risk in women using HRT who undergo elective surgery compared with non-users.[122,123] Importantly, as with any surgery, mechanical and pharmacological prophylaxis should be used appropriately in these patients (Figure 1).

Conclusions

The risk of VTE throughout a woman's life is associated primarily with hormonal exposure. Use of OCPs in young adulthood with the development of VTE may reveal inherited thrombophilia. Pregnancy and particularly the post-partum period, confer the greatest risk of VTE, but this risk must be put in context of the low overall absolute complication rate. Guidelines for prevention of VTE during pregnancy are based on history of VTE, family history, and known inherited thrombophilia. Use of HRT may be safest if given as an estrogen-only preparation to young postmenopausal women for less than 5 years. Universal screening for thrombophilia that may heighten awareness of VTE is not recommended; however, selected testing in high-risk groups may be warranted. The lack of firm recommendations for prevention of VTE in women highlights the need for future investigation aimed at identifying high-risk groups and evaluating safety and efficacy of prophylactic measures.

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