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REVIEW ARTICLE

Sex matters: Practice 5P's when treating young women with venous thromboembolism

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Abstract

Sex matters when it comes to venous thromboembolism (VTE). We defined 5P's – period, pill, prognosis, pregnancy, and postthrombotic syndrome – that should be discussed with young women with VTE. Menstrual blood loss (Period) can be aggravated by anticoagulant therapy. This seems particularly true for direct oral anticoagulants. Abnormal uterine bleeding can be managed by hormonal therapy, tranexamic acid, or modification of treatment. The use of combined oral contraceptives (Pill) is a risk factor for VTE. The magnitude of the risk depends on progestagen types and estrogen doses used. In women using therapeutic anticoagulation, concomitant hormonal therapy does not increase the risk of recurrent VTE. Levonorgestrel-releasing intrauterine devices and low-dose progestin-only pills do not increase the risk of VTE. In young women VTE is often provoked by transient hormonal risk factors that affects *prognosis*. Sex is incorporated as predictor in recurrent VTE risk assessment models. However, current guidelines do not propose using these to guide treatment duration. Pregnancy increases the risk of VTE by 4-fold to 5-fold. Thrombophilia and obstetric risk factors further increase the risk of pregnancy-related VTE. In women with a history of VTE, the risk of recurrence during pregnancy or post partum appears to be influenced by risk factors present during the first VTE. In most women with a history of VTE, antepartum and postpartum thromboprophylaxis with low-molecular-weight heparin is indicated. Women generally are affected by VTE at a younger age then men, and they have to deal with long-term complications (Post-thrombotic syndrome) of deep vein thrombosis early in life.

KEYWORDS

anticoagulants, contraceptives, female, pregnancy, venous thromboembolism

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1 | INTRODUCTION

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism, is the third most frequent cardiovascular disease.[1] For several aspects of VTE, sex matters. Risk factors, presenting location, side effects related to treatment, optimal treatment duration, and prognosis differ between men and women.[2–4]

Several studies have estimated the incidence of VTE in the general population to be approximately 1 per 1000 person-years.[5–8] However, the incidence of VTE differs between men and women and per age group. Women are at higher risk during fertile ages, whereas men are at higher risk after the age of 50 years (Figure A1). This difference can be explained by female-specific transient risk factors, such as pregnancy and hormone use.[9] Interestingly, men seem to have a higher intrinsic risk of VTE than women; the risk of a first VTE in men is higher if hormonal risk factors are not taken into account,[9] after the age of 50 years,[5] and they have a higher recurrence rate of VTE regardless of reproductive risk factors.[10]

In this case-based review we will discuss five female-specific themes for practice, which we defined as the 5P's: period, pill, prognosis, pregnancy, and postthrombotic syndrome. The 5P's should be discussed when treating young women who suffer from VTE, because sex really matters.

2 | PERIOD

Anticoagulant treatment increases the risk of bleeding. In premenopausal women, menstrual bleeding can be aggravated by the use of anticoagulants. Abnormal uterine bleeding (AUB) includes heavy menstrual bleeding, which is defined as a combination of unpredictability, excessive duration, abnormal volume, or abnormal frequency of the menses.[11] Confusingly, studies evaluating menstrual bleeding patterns use the terms AUB, heavy menstrual bleeding and menorrhagia interchangeably; and we refer to the terms used by the authors in the original publications.

CASE, BOX 1

Our case is a 24-year old woman, who has been taking third-generation combined oral contraceptives for management of heavy menstrual bleeding since the age of 16. She has a positive family history for VTE: her mother had postpartum DVT and her grandmother died of pulmonary embolism after hip replacement surgery. Our patient had recently been on a long-haul flight of 9 h and had progressive complaints of a painful, warm, and swollen left leg.

Her mother recognized symptoms of DVT and sent her to the emergency department. On physical examination, an edematous left leg was seen. The calf circumference was 4 cm larger compared to the right side, and there was pain with calf compression. Vital signs were normal. Compression ultrasound examination of the leg confirmed DVT in the left popliteal and femoral veins. The patient was treated with a direct oral anticoagulant (DOAC) and received elastic compression stockings to reduce swelling. We recommended that she continue the oral contraceptive pill while taking anticoagulants.

CASE, BOX 2

Three weeks aft.er the diagnosis, our patient visited the outpatient clinic for a routine follow-up. Her leg symptoms had decreased and on physical examination there were no signs of remaining edema. She had discontinued the oral contraceptive pill as she was frightened by her DVT. She reported that her first menstrual period after start of anticoagulant treatment had lasted for 10 days and she had had to change sanitary napkins every 2 h.

In women treated with vitamin K antagonists (VKAs), cohort studies reported incidences of heavy menstrual bleeding between 22% and 71%.[12–14] The DOACs are now the preferred treatment for VTE because of a lower incidence of major and fatal bleeding as compared to VKA.[15]

In a post hoc analysis of the EINSTEIN studies, menstrual bleeding was evaluated in 1737 women younger than 60, of whom 463 used concomitant hormonal therapy. Abnormal uterine bleeding occurred more frequently in women treated with rivaroxaban than VKA hazard ratio 2.1; 95% confidence interval [CI] 1.6-2.9).[16] Rates of AUB did not differ between apixaban and VKA (odds ratio [OR] 1.2; 95% CI 0.7-2.0) in the AMPLIFY trial (n = 2228), but clinically relevant non-major bleeding was more likely to be of vaginal origin with apixaban (45%) than with warfarin (20%).[17] The HOKUSAI-VTE study (n = 1293) found an increased risk of AUB in the edoxaban group compared with the VKA group (hazard ratio 1.9; 95% CI 1.1-2.5).[18] An individual patient data meta-analysis of the phase 3 trials showed that major bleeding of vaginal origin, although rare, occurred more often with use of factor Xa-inhibitor than with VKA (17/10595 vs. 3/10957).[19] In contrast, data from the pooled RE-COVER and RE-MEDY trials (n = 1280), in which the effect of direct thrombin inhibitor dabigatran was evaluated, showed an overall AUB rate of 5.9% with dabigatran, compared to 9.6% with VKA (OR 0.6; 95% CI 0.4-0.9).[20]

To our knowledge, there are no studies that report data on menstrual bleeding patterns in women treated with unfractionated heparin or low-molecular-weight heparin (LMWH). Treatment duration with unfractionated heparin or LMWH is relatively short and prescribed in a prophylactic dosage in the majority of patients. Patients of fertile age treated with therapeutic-dose LMWH often are pregnant patients or patients treated for cancer. In these populations, menstrual blood loss is either absent or a non-issue.

2.1 | Management of abnormal uterine bleeding

Abnormal uterine bleeding is chronic in nature and it negatively impacts quality of life.[21] Therefore, adequate treatment is

imperative. A step-by-step assessment and management strategy in women using anticoagulants was recently discussed by Boonyawat and colleagues.[22] They suggest that clinical assessment includes at least evaluation of anticoagulant therapy intensity, need for ongoing anticoagulation (see also paragraph in Section 4) and evaluation of anemia and iron status.[22] Referral to a gynecologist is mandatory when additional underlying uterine abnormalities are suspected.[23]

Suggested management options encompass 3 main potential approaches: (a) hormonal therapy, (b) tranexamic acid and (c) modification of anticoagulant therapy. Table A1 displays an evidence-based summary of management strategies for abnormal vaginal bleeding during anticoagulant treatment.

2.1.1 | Hormonal therapy

Oral contraceptives can be used to regulate or postpone periods but increase the risk of VTE among women who are not on anticoagulant therapy.[24] The risk of recurrent VTE did not differ between women with and without hormonal contraceptives during anticoagulant treatment in a post-hoc analysis of the EINSTEIN studies (respectively 3.7%/year vs. 4.7%/year, adjusted hazard ratio 0.6; 95% CI 0.2-1.4).[16] Hence, it is our practice to continue oral contraceptives in women with acute VTE who are starting with anticoagulant treatment, and to discontinue prior to stopping anticoagulant treatment.

The levonorgestrel-releasing intrauterine device (IUD) is an effective contraceptive method that reduces the amount and duration of menstrual bleeding in the general population.[25] Large cohort studies demonstrated that the IUD does not increase the risk of first VTE.[26–28] One randomized controlled trial (n = 40) reported the IUD to be effective in management of AUB in women treated with VKA after heart valve replacement. Menstrual blood per cycle as assessed by the pictorial blood loss assessment chart decreased in patients treated with the IUD from 239 to 155 points in 6 months, whereas no significant changes were observed in controls.[29]

2.1.2 | Tranexamic acid

Antifibrinolytic agents, such as tranexamic acid, reduce menstrual blood loss up to 50%, but have no effect on duration of bleeding.[30] Current guidelines recommend a dose of 1-1.5 g three to four times a day for 3 to 4 days, starting on the first day of the menstrual period.[31] Considering the mechanism of action of tranexamic acid, concerns have been raised with regard to potential thromboembolic, and active thromboembolic disease is stated as a contraindication for treatment with tranexamic acid.[32] The safety of tranexamic acid administration in patients with recent VTE has never been evaluated, but in large placebo-controlled randomized controlled trials in other prothrombotic settings such as major trauma and postpartum hemorrhage no increase in VTE was observed with use of tranexamic acid.[33,34]

CASE, BOX 3

During the next routine visit 3 months after VTE, our patient reported that her period had worsened. We discussed treatment options and as our patient was also seeking a long-term contraceptive method, she chose a levonorgestrel-containing IUD.

2.1.3 | Modification of DOAC dose

In the first 3 months of treatment the risk of extension or recurrence of VTE likely outweighs the benefit of reduced heavy menstrual bleeding. However, after this time, a temporary dose reduction of rivaroxaban or interruption of anticoagulation for the first days of the menstrual period was found to decrease menstrual bleeding without increasing risk of VTE.[35] Switching treatment from a factor Xa inhibitor to dabigatran may be a reasonable option with regard to heavy menstrual bleeding but requires further investigation.[20]

3 | PILL

Oral contraceptives are used by 8% to 37% of women of fertile age.[36–38] The use of combined oral contraceptives is a well-established risk factor for VTE. In a recent Cochrane review, results of 15 studies were synthesized: The VTE risk is highest during the first months and gradually decreases during the first year, but even after long-term exposure to combined oral contraceptives, women remain at three to eight times increased risk of VTE compared to non-users.[39] Therefore, women with a personal history of VTE who have discontinued anticoagulant treatment should not use oral contraceptives. Hence, prior to cessation of anticoagulant treatment, contraceptive methods that are safe with regard to thromboembolic complications should be discussed. Table A2 summarizes the VTE risk with various hormonal contraceptive methods.

The impact of combined oral contraceptives is higher in women who have risk factors of VTE, such as thrombophilia or a positive family history (i.e., first degree relative) of VTE.[3] The increase in risk of VTE depends on both estrogen doses and synthetic progestogen types used (Table A2).[39,40] These risk increases should be considered in the context of the estimated 2 to 3 per 10 000 per year absolute

CASE, BOX 4

The younger sister of the patient also visited our clinic. She had been taking combined oral contraceptives for some years now. But because of her family history, she became afraid of developing VTE when continuing the pill. She wanted to know about other effective contraceptive options with less risk of thromboembolic complications.

risk of VTE in young women in the general population.[5] As the risk of VTE increases with age, the impact of combined oral contraceptives exponentially increases with age.[5]

For young women with thrombophilia, Table A3 provides crude estimates of the absolute risk of first VTE with the use of second-generation or third-generation combined oral contraceptives. These risk estimates help to counsel women and assess risk benefit in individuals with known thrombophilia or a positive family history of VTE. In our view, a family history for VTE alone is not an absolute contraindication against hormonal contraceptives. In women who have families with VTE and strong thrombophilias or who have other risk factors (e.g., obesity, increasing age, cancer, prolonged immobilization), we suggest considering alternative contraceptive methods.

4 | PROGNOSIS

The impact of a first VTE unfortunately goes beyond the symptoms and burden of initial treatment of the event. Important aspects of the prognosis of VTE include risk of recurrence and bleeding associated with anticoagulant treatment.

After the initial treatment period of 3 months, decisions regarding continuation of anticoagulant therapy have to be made.[41] To do so, the risk of recurrence and the risk of bleeding on anticoagulant therapy should be weighed carefully.[15] The risk of recurrence is lowest after provoked VTE. The stronger the provoking risk factor at time of the first event, the lower the risk of recurrence, whereas patients with an unprovoked event have a high risk of recurrence.[42,43] Furthermore, women have a lower risk of recurrence than men.[10,44] In an individual patient data meta-analysis including data from seven studies, a total of 1268 women with a first VTE were followed after cessation of anticoagulant therapy.[44] The overall estimated recurrence rates after 1 year were 5.3% (95% CI 4.1-6.7) and 9.1% (95% CI 7.3-11.3) after 3 years.[44] Women with unprovoked VTE (i.e. no risk factor) seem at highest risk of recurrence: 6.7% (95% 4.9-9.2) after 1 year and 10.6% (95% 8.1-13.8) after 3 years.[44] Among women without a major provoking risk factor, those with hormone-associated VTE had a lower risk of recurrent VTE than those with an unprovoked event (hazard ratio 0.5 95% CI 0.3-0.8).[44] In a cohort study including 289 women with a first unprovoked VTE who had been treated at least 3 months with VKA, after 10 years the cumulative incidence of a recurrence was 18% (95% CI 14-23).[45] Of note, hormone-related or estrogen-related VTE in some studies is not regarded as a provoking factor and hence included under the definition of unprovoked VTE.

CASE, BOX 5

Our patient has been treated with anticoagulants for 3 months. Her DVT was provoked, so we advised her to discontinue anticoagulant treatment. Although she felt relieved that anticoagulant therapy could be stopped, she was also concerned about recurrent thromboembolic events and asked us about her personal risk of recurrence.

The risk of major bleeding while on anticoagulant therapy has been estimated to be 1% to 3% per year,[46,47] and female sex is considered a risk factor.[48] Nevertheless, in randomized controlled trials bleeding rates are often not reported separately for men and women. This is of concern, as there seems to be a sex difference in the composite of major and clinically relevant non-major bleeding. In the HOKUSAI and EINSTEIN trials, women treated for acute VTE had a higher risk of major and clinically relevant non-major bleeding than men (Figure A2).[49–51] Combined rates of major and clinically relevant non-major bleeding were not reported separately for men and women in the RECOVER I and II and AMPLIFY trials.

When deciding whether a patient will benefit from extended anticoagulant treatment, ideally the risk of both recurrent VTE and bleeding is known, both on and off treatment. In three large trials the efficacy and safety of extended dabigatran (full dose, 150 mg twice daily, compared with warfarin or placebo),[52] apixaban (full dose 5 mg twice daily and reduced dose 2.5 mg twice daily compared with each other and placebo)[53] and rivaroxaban (full dose 20 mg once daily and reduced dose 10 mg once daily compared with aspirin 100 mg once daily)[54] have been assessed. In these studies very few young women with hormone-associated VTE were included or little information on this group was provided. Although it is unlikely that there is a differential effect of extended anticoagulant treatment, the benefit of (reduced-dose) extended treatment of VTE in young women with a (hormone-provoked) first event is not well studied. In addition, it is uncertain whether a reduced-dose strategy is sufficiently safe regarding the risk of VTE recurrence in women who decide to continue hormones concomitantly (also see the Section 2).

Current guidelines do not propose sex-specific management strategies. In general, it is recommended to discontinue anticoagulation after 3 months in cases of VTE provoked by a major transient risk factor. In patients with a first unprovoked VTE and a low or moderate bleeding risk, indefinite duration of anticoagulant therapy is suggested.[15]

Indeed, patients with an unprovoked event are at highest risk of recurrence; however, a more accurate and refined method to aid patients and their physicians to decide whether to continue or discontinue anticoagulant therapy is needed. Clinical prediction models or risk assessment models are promising tools but are not yet implemented or suggested by major guidelines. Over the past years several of such models have been developed. Most incorporate sex as a predictor, where female sex overall is associated with lower recurrence risk. Before these risk assessment models can be implemented in practice, robust validation and preferably evaluation in clinical trials are needed.

One model, the HERDOO2 model, was specifically designed for women with unprovoked VTE, as in this strategy all men should continue anticoagulants.[55] Interestingly, although oral contraceptive use and hormone use meet all criteria for a provoking risk factor, in this study hormone-related VTE was considered as unprovoked.[56] The model contains seven predictors: hyperpigmentation, edema, or redness

in either leg; D-dimer level ≥250 μg/L; body mass index ≥30; and age ≥65 years; it was recently prospectively validated.[57] Of 1213 women, 631 (51.3%) were classified as low risk. Of these, 591 discontinued anticoagulant treatment. After a total of 564 person-years 17 recurrences occurred in this low risk group, that is, an annual incidence rate of 3.0% (95% CI 1.8-4.8). In the high-risk group, 101 women discontinued anticoagulants; the annual rate of recurrence was 7.4% (95% 3.0-15.2).[56] In the high risk-group that included men and women (and was not specified separately) who continued anticoagulants, the risk of recurrence was 1.6% (1.1-2.3) per year and the annual risk of major bleeding was 1.2% (0.8%-1.8%). Of note, given the controversy of the definition of unprovoked VTE, we would have been interested to assess the risk of recurrent VTE in women with a hormone-provoked first VTE after discontinuation of anticoagulants, but these data cannot be derived from this study. There are also limitations in the generalizability of the study, such as that the majority of patients were of Caucasian descent and were on VKA, and a specific D-dimer assay (VIDAS®) was used.[55,57,58]

In summary, we consider use of hormonal oral contraceptives a transient provoking risk factor, and we advise a duration of anticoagulant treatment of 3 months and replacement of oral contraceptives by a safe alternative method shortly prior to discontinuing anticoagulant therapy. In absence of provoking risk factors, we advise extending anticoagulant treatment if the bleeding risk is low but take individual preference into account. Since the risk of recurrence in women with provoked events is not negligible, future well-validated risk assessment strategies are necessary to aid patients and physicians to make informed decisions. For women, we advise contacting their physician when planning pregnancy (also see the Section 5).

5 | PREGNANCY

During pregnancy, the risk of VTE is 4-5-fold higher than in non-pregnant women of the same age.[59] The pregnant body is exposed to major hemodynamic changes and hemostatic challenges. Especially peripartum there is a significant risk of bleeding. In response to this risk, the body shifts to a procoagulant state during pregnancy and puerperium: plasma levels of procoagulant factors are elevated,[60,61] while natural anticoagulant activity (reduced levels of protein S and an acquired resistance to protein C) is decreased.[61,62] The procoagulant state, along with reduced flow in the lower extremities and venous stasis caused by pressure of the gravid uterus on the inferior vena cava and the aggravation of the crossing of the left iliac artery over the left iliac vein,[63] as well as delivery-associated vascular injury contribute to the increased risk of VTE in pregnancy and puerperium. In absolute terms: 1 to 2 per 1000 pregnancies are complicated by VTE [64,65] with a case fatality rate of 0.41%.[66] In a World Health Organization systematic analysis, haemorrhage (16.3%, 95% CI 11.1-24.6) was found to be the leading direct cause of maternal death in developed countries, followed by VTE, accountable for 13.8% (95% CI 10.1-22.0) of maternal deaths.[67]

Women with a personal history of VTE are at high risk of recurrence during subsequent pregnancy and the postpartum period. The absolute risk of recurrence without pharmacologic prophylaxis is estimated at 6% to 10% during subsequent pregnancy.[59,68–70] Of pregnancy-related events, approximately half occur during pregnancy and half in the 6 weeks postpartum.[64] Given the longer duration of pregnancy than the postpartum period, the absolute daily risk of recurrent VTE is highest post partum. Moreover, the risk of recurrence appears to be influenced by the factors present during the first VTE: unprovoked VTE or VTE provoked by non-estrogen transient risk factors is associated with lower risk of recurrence than hormonally-related or pregnancy-related VTE.[68,69,71,72] Hence, patients who had a single VTE that was associated with a transient non-hormonal risk factor alone are considered at low risk of recurrence.[73,74] For these patients, the burden of self-injecting, side effects, and risk of peripartum bleeding may not outweigh the high number needed to treat during pregnancy, and only postpartum thromboprophylaxis for 6 weeks is recommended.[73,74] In all other pregnant women with a history of VTE, that is, unprovoked VTE, VTE associated with hormonal risk factors, or recurrent VTE but no indication for anticoagulation outside pregnancy, both antepartum and postpartum prophylaxis are suggested.[73]

The most important strategy to reduce the risk of recurrence during pregnancy consists of prophylaxis with heparin (either unfractionated heparin or LMWH), which is the only anticoagulants that does not cross the placenta and is thus safe during pregnancy.[75] Data from studies in which LMWH was directly compared to unfractionated heparin in the non-pregnant population demonstrate similar efficacy and a superior safety profile of LMWH.[77,78] From the pregnant population, only observational data with similar observations are available.[79–82] The LMWH has a lower risk of osteoporosis and heparin-induced thrombocytopenia.[73]

The optimal dose of LMWH for prevention of pregnancy-related recurrent VTE has not been adequately investigated. Data from retrospective cohort studies suggest high recurrence rates ranging from 2.5% to 8% of VTE despite thromboprophylaxis.[68,69,83–85]

CASE, BOX 6

A couple of years after her deep vein thrombosis, the patient visited our antenatal clinic because she and her husband were planning pregnancy. They were well aware of the VTE risk during pregnancy and wanted to discuss the optimal strategy at the beginning.

Soon after the IUD had been removed, the patient became pregnant. She participated in the Highlow study (NCT01828697) and was randomized to the weight-adjusted intermediate-dose LWMH. Injecting LMWH caused several bruises and sometimes infiltrates at injection sites, but no serious bleeding occurred. After 38 weeks of pregnancy, she gave birth to a healthy son. She continued thromboprophylaxis until 6 weeks post partum. She did not experience recurrent VTE.

Only two small randomized controlled trials (n = 16 and n = 40), comparing LMWH with placebo or no treatment, have been conducted.[86,87] In the absence of high-quality evidence, the American College of Chest Physicians (ACCP) guideline suggests use of either prophylactic or intermediate (half of therapeutic) dose, with no preference for one dose over the other,[73] whereas the American Society of Hematology (ASH) VTE guideline suggests a prophylactic dose antepartum and has a conditional recommendation against the intermediate dose.[74] During the postpartum period both guidelines suggest either low-dose or intermediate-dose thromboprophylaxis.[73,74] Since 2013, the Highlow study (NCT01828697), an international, multicenter, randomized controlled trial, comparing low-dose with intermediate dose LWMH for the prevention of pregnancy-related recurrent VTE, is ongoing.[88] To date, > 815 patients have been recruited and results are expected in 2021.

In women without a personal history of VTE, thromboprophylaxis is suggested in those at a particular high risk of VTE only, such as those with both thrombophilia and a positive family history of VTE.[73,74] We have recently reviewed the use of anticoagulation for specific situations such as some types of hereditary thrombophilia and other risk factors for VTE (e.g. cesarean delivery, pregnancy complications, obesity, postpartum hemorrhage) in detail elsewhere.[89] Of note, in the ASH VTE guidelines some of the recommendations have changed as compared to the ACCP guidelines.[74] In Table A4, the recommendations of ASH and ACCP guidelines with regard to antepartum and postpartum thromboprophylaxis for various forms of thrombophilia are summarized.

Women who are planning pregnancy while using anticoagulants should be informed about the possible teratogenic effects of their therapy. Given the lack of solid data on the risk of exposure to DOAC in very early pregnancy, the Women's Health Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis recommends switching women who use DOACs to VKA or therapeutic-dose LMWH preconceptionally.[90] As VKAs are teratogenic, women should be switched to LMWH as soon as the pregnancy test result is positive and prior to 6 weeks of gestation, since the embryo is most vulnerable for vitamin K depletion in the 6th to 12th week of gestation.[91] Also, the effect of VKA should be reversed by oral vitamin K supplements.[73] The decision to prefer VKA to LMWH is influenced by the uncertain time to conception and the side effects of long-term use of LMWH. Some clinicians and patients prefer to switch directly from DOAC to LMWH after a positive pregnancy test, although data on safety of DOAC in very early pregnancy are extremely scarce.[92] In those cases, we recommend reporting the DOAC exposure in early pregnancies to the International Society of Thrombosis and Haemostasis registry.[93]

When (first or recurrent) VTE occurs during pregnancy, treatment with therapeutic-dose anticoagulants should be started promptly and continued for at least 3 months and until 6 weeks after delivery, since the risk of (recurrent) VTE remains elevated during pregnancy and the postpartum period.[73,76,94] Monitoring of drug levels or anticoagulant effect is generally not necessary for LMWH[74]; exceptions are patients with renal impairment, extreme body weight or recurrent VTE while receiving therapeutic-dose anticoagulation.[76] No studies have evaluated whether dose reduction after an initial 3-month treatment period of therapeutically dosed LMWH is safe. In the postpartum period, both LMWH and VKA can be used safely while breastfeeding[73,95] whereas DOACs are contraindicated.[90]

Around delivery, anticoagulant treatment has to be interrupted in order to minimize delivery-related bleeding, or to assure safe performance of cesarean delivery or application of neuraxial anesthesia. Peripartum management requires a multidisciplinary approach: the risk of bleeding, risk of VTE, and risk of other complications have to be taken into account. We have recently discussed considerations and recommendations elsewhere.[89]

6 | POST-THROMBOTIC SYMPTOMS

As with every disease, not only the acute symptoms, but also the long-term complications are of great importance to patients. Sex is not an independent risk factor for the development of PTS.[96] However, since women are often affected by VTE at younger age than men,[5] they have to deal with long-term complications earlier in life.

Postthrombotic syndrome is thought to be caused by venous hypertension;[97] it includes subjective and objective changes of the leg leading to discomfort, physical impairment and esthetic problems. Signs and symptoms comprise pain, cramps, heavy feeling of the legs, pruritus, paresthesia, pretibial edema, venous ectasia, hyperpigmentation, skin induration and in the most severe cases leg ulcers.

The prevalence of PTS is 20% to 50% up to 8 years after acute DVT.[98–100] In pregnancy-related DVT, the femoral and iliac veins are involved more often (72%) than in non-pregnant DVT patients (9%)[101,102] In a Norwegian cohort study of 204 women with pregnancy-related DVT and a follow up of 3 to 16 years, 85 (42%) reported PTS; PTS was severe in 7%.[103] Proximal location of postpartum DVT was the most important predictor for PTS, which

leads to an impaired Quality of life (QoL).[107] In a Swedish cohort consisting of 1040 women with a first episode of VTE, QoL was severely impaired in patients who developed PTS compared to controls unexposed to VTE. In a cohort of 559 pregnant patients with pregnancy-related DVT, the known effect on QoL was confirmed: women who developed PTS during pregnancy seemed to have poorer QoL 3 to 16 years after DVT than controls who did not have DVT.[109] Moreover, they suffered from impaired general health due to pain and skin and psychiatric problems.[109] Patients with pregnancy-related DVT but no PTS evaluated their QoL and general health similarly to controls.

Whether PTS can be prevented by elastic compression stockings in patients with DVT is a matter of debate, and the American Heart Association guidelines give a weak (class IIB) recommendation against routine use of elastic compressions stockings.[96] In

CASE, BOX 7

Even though our patient's DVT was treated adequately, her complaints have never fully resolved: after a day of work at the ward, her leg is often swollen, and feels heavy and tired. She also suffers from nocturnal cramps. Apart from the edema, her leg looks slightly darker and prominent varices are visible. Postthrombotic syndrome (Villalta score 9) was diagnosed, and the patient was recommended to wear elastic compression stockings.

our practice we prescribe initial and individualized compression therapy.[110] Catheter-directed thrombolysis for extensive proximal DVT does not unequivocally reduce the risk of PTS or improve QoL, while it increases bleeding risk.[105,106] Postthrombotic syndrome cannot be cured. Although the role of elastic compression stockings for the prevention of PTS is undecided, compression-based therapies can be beneficial in reduction of symptoms such as edema, heaviness of the leg, and discomfort.[104]

7 | SUMMARY

When treating young women with VTE, it is essential to acknowledge sex-specific differences. Female-specific aspects of the disease and its treatment should be considered. In this review we propose to use a mnemonic of the 5P's that should be discussed: menstrual blood loss during **periods** can be aggravated when using anticoagulants, the **pill** is contraindicated after VTE and safe contraceptive methods should be offered, the **prognosis** of recurrent VTE after cessation of anticoagulant treatment is different from that of men given the presence of other transient risk factors, thromboprophylaxis for prevention of **pregnancy**-related recurrence is indicated in all patients with a personal history of VTE, and **PTS** can develop early in life and impair QoL.

CONFLICT OF INTERESTS

Ingrid Bistervels and Saskia Middeldorp are investigators of the Highlow study, a randomized controlled trial comparing low-dose LMWH with intermediate-dose LMWH in pregnant women with a history of VTE (http://www.ClinicalTrials.gov; NCT01828697). Saskia Middeldorp reports grants and fees paid to her institution from GSK, BMS/Pfizer, Aspen, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Sanofi, and Portola.

AUTHOR CONTRIBUTIONS

Ingrid Bistervels, Luuk Scheres, and Eva Hamulyák drafted the first version of the manuscript. All authors contributed to revising previous versions and approved the final version of the manuscript.

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REFERENCES

1. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363–71.
2. Scheres LJJ, Brekelmans MPA, Beenen LFM, Buller HR, Cannegieter SC, Middeldorp S. Sex-specific differences in the presenting location of a first venous thromboembolism. J Thromb Haemost. 2017;15(7):1344–50.
3. Bleker SM, Coppens M, Middeldorp S. Sex, thrombosis and inherited thrombophilia. Blood Rev. 2014;28(3):123–33.
4. Healy B. The Yentl syndrome. N Engl J Med. 1991;325(4):274–6.
5. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692–9.
6. Delluc A, Tromeur C, Le Ven F, Gouillou M, Paleiron N, Bressollette L, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. Thromb Haemost. 2016;116(5):967–74.
7. Kort D, van Rein N, van der Meer FJM, Vermaas HW, Wiersma N, Cannegieter SC, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. J Thromb Haemost. 2017;15(12):2352–60.
8. Heit JA, Ashrani A, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thromb Haemost. 2017;117(2):390–400.
9. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S. Sex difference in risk of second but not of first venous thrombosis: paradox explained. Circulation. 2014;129(1):51–6.
10. Roach RE, Lijfering WM, Tait RC, Baglin T, Kyrle PA, Cannegieter SC, et al. Sex difference in the risk of recurrent venous thrombosis: a detailed analysis in four European cohorts. J Thromb Haemost. 2015;13(10):1815–22.
11. Munro MG, Critchley HO, Broder MS, Fraser IS. Disorders FWGoM. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.
12. Peake LJ, Grover SR, Monagle PT, Kennedy AD. Effect of warfarin on menstruation and menstrual management of the adolescent on warfarin. J Paediatr Child Health. 2011;47(12):893–7.
13. De Crem N, Peerlinck K, Vanassche T, Vanheule K, Debaveye B, Middeldorp S, et al. Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. Thromb Res. 2015;136(4):749–53.
14. Sjalander A, Friberg B, Svensson P, Stigendal L, Lethagen S. Menorrhagia and minor bleeding symptoms in women on oral anticoagulation. J Thromb Thrombolysis. 2007;24(1):39–41.
15. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52.
16. Martinelli I, Lensing AW, Middeldorp S, Levi M, Beyer-Westendorf J, van Bellen B, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood. 2016;127(11):1417–25.

17. Brekelmans MP, Scheres LJ, Bleker SM, Hutten BA, Timmermans A, Buller HR, et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. Thromb Haemost. 2017;117(4):809–15.
18. Scheres L, Brekelmans M, Ageno W, Ay C, Buller HR, Eichinger S, et al. Abnormal vaginal bleeding in women of reproductive age treated with edoxaban or warfarin for venous thromboembolism: a post hoc analysis of the Hokusai-VTE study. BJOG. 2018;125(12):1581–9.
19. Bleker SM, Brekelmans MPA, Eerenberg ES, Cohen AT, Middeldorp S, Raskob G, et al. Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists. Thromb Haemost. 2017;117(10):1944–51.
20. Huisman MV, Ferreira M, Feuring M, Fraessdorf M, Klok FA. Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism. J Thromb Haemost. 2018;16(9):1775–8.
21. Godin R, Marcoux V, Tagalakis V. Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism. Vascul Pharmacol. 2017;93–95:1–5.
22. Boonyawat K, O'Brien SH, Bates SM. How I treat heavy menstrual bleeding associated with anticoagulants. Blood. 2017;130(24):2603–9.
23. Klok FA, Schreiber K, Stach K, Ageno W, Middeldorp S, Eichinger S, et al. Oral contraception and menstrual bleeding during treatment of venous thromboembolism: expert opinion versus current practice: combined results of a systematic review, expert panel opinion and an international survey. Thromb Res. 2017;153:101–7.
24. Fraser IS, Romer T, Parke S, Zeun S, Mellinger U, Machlitt A, et al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial. Hum Reprod. 2011;26(10):2698–708.
25. Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev. 2015;4:CD002126.
26. van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol. 2010;30(11):2297–300.
27. Lidegaard O, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ. 2012;344:e2990.
28. Bergendal A, Persson I, Odeberg J, Sundstrom A, Holmstrom M, Schulman S, et al. Association of venous thromboembolism with hormonal contraception and thrombophilic genotypes. Obstet Gynecol. 2014;124(3):600–9.
29. Kilic S, Yuksel B, Doganay M, Bardakci H, Akinsu F, Uzunlar O, et al. The effect of levonorgestrel-releasing intrauterine device on menorrhagia in women taking anticoagulant medication after cardiac valve replacement. Contraception. 2009;80(2):152–7.
30. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018;4:CD000249.
31. NICE guideline. Heavy menstrual bleeding. London, UK: National Institute for Health and Clinical Excellence. NICE Guidelines; update March 2018. 2018.
32. European Medicines Agency. Antifibrinolytics containing aprotinin, aminocoproic acid and tranexamic acid. Assessment report. https://www.ema.europa.eu/documents/referral/assessment-report-antifibrinolytic-medicines-tranexamic-acid_en.pdf2012
33. Woman Trial Collaborators; Shakur H, Roberts I, Fawole B, Chaudhri R, El-Sheikh M, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105–16.
34. CRASH-2 Trial Collaborators; Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23–32.
35. Boonyawat KL A., Prins M., Prandoni P., Weitz J.I., Crowther M. Menstrual bleeding patterns in women treated with rivaroxaban: Data from the EINSTEIN CHOICE trial. Paper presented at the XXVI Congress of the International Society on Thrombosis and Haemostasis. 8-13 July 2017. Berlin, Germany 2017.
36. United Nations. World Contraceptive Use 2018. Department of Economic and Social Affairs, Population Division. 2018.
37. Scheres LJJ, Lijfering WM, Cannegieter SC. Current and future burden of venous thrombosis: not simply predictable. Res Pract Thromb Haemost. 2018;2(2):199–208.
38. Christin-Maitre S. History of oral contraceptive drugs and their use worldwide. Best Pract Res Clin Endocrinol Metab. 2013;27(1):3–12.
39. de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014;(3):CD010813.
40. Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ. 2013;347:f5298.
41. Middeldorp S. Duration of anticoagulation for venous thromboembolism. BMJ. 2011;342:d2758.
42. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003;362(9383):523–6.
43. Prins MH, Lensing AWA, Prandoni P, Wells PS, Verhamme P, Beyer-Westendorf J, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv. 2018;2(7):788–96.
44. Douketis J, Tosetto A, Marcucci M, Baglin T, Cosmi B, Cushman M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ. 2011;342:d813.
45. Kyrle PA, Kammer M, Eischer L, Weltermann A, Minar E, Hirschl M, et al. The long-term recurrence risk of patients with unprovoked venous thromboembolism: an observational cohort study. J Thromb Haemost. 2016;14(12):2402–9.
46. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med. 2003;139(11):893–900.
47. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968–75.
48. Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med. 1999;159(5):457–60.
49. Investigators E, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–510.
50. Investigators E-P, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.
51. Hokusai VTEI, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406–15.

52. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709–18.
53. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699–708.
54. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med. 2017;376(13):1211–22.
55. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ. 2008;179(5):417–26.
56. Middeldorp S, Iorio A. Oral contraceptive use is a provoking factor for venous thromboembolism. BMJ. 2017;357:j2073.
57. Rodger MA, Le Gal G, Anderson DR, Schmidt J, Pernod G, Kahn SR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ. 2017;356:j1065.
58. Rodger MA, Le Gal G, Langlois NJ, Gin B, Mallick R, Giulivi A, et al. "HERDOO2" clinical decision rule to guide duration of anticoagulation in women with unprovoked venous thromboembolism. Can I use any d-Dimer? Thromb Res. 2018;169:82–6.
59. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006;194(5):1311–5.
60. Brenner B. Haemostatic changes in pregnancy. Thromb Res. 2004;114(5–6):409–14.
61. Clark P, Brennand J, Conkie JA, McCall F, Greer IA, Walker ID. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. Thromb Haemost. 1998;79(6):1166–70.
62. Franchini M. Haemostasis and pregnancy. Thromb Haemost. 2006;95(3):401–13.
63. Taylor J, Hicks CW, Heller JA. The hemodynamic effects of pregnancy on the lower extremity venous system. J Vasc Surg Venous Lymphat Disord. 2018;6(2):246–55.
64. Kourlaba G, Relakis J, Kontodimas S, Holm MV, Maniadakis N. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. Int J Gynaecol Obstet. 2016;132(1):4–10.
65. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143(10):697–706.
66. Abbasi N, Balayla J, Laporta DP, Kezouh A, Abenhaim HA. Trends, risk factors and mortality among women with venous thromboembolism during labour and delivery: a population-based study of 8 million births. Arch Gynecol Obstet. 2014;289(2):275–84.
67. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
68. De Stefano V, Martinelli I, Rossi E, Battaglioli T, Za T, Mannuccio Mannucci P, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol. 2006;135(3):386–91.
69. Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost. 2005;3(5):949–54.
70. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism: recurrence of clot in this pregnancy study group. N Engl J Med. 2000;343(20):1439–44.
71. White RH, Chan WS, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb Haemost. 2008;100(2):246–52.
72. Lazo-Langner A, Al-Ani F, Weisz S, Rozanski C, Louzada M, Kovacs J, et al. Prevention of venous thromboembolism in pregnant patients with a history of venous thromboembolic disease: a retrospective cohort study. Thromb Res. 2018;167:20–5.
73. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e691S–736S.
74. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2(22):3317–59.
75. Richter C, Sitzmann J, Lang P, Weitzel H, Huch A, Huch R. Excretion of low molecular weight heparin in human milk. Br J Clin Pharmacol. 2001;52(6):708–10.
76. Gynaecologists RCOG. Thrombosis and Embolism during Pregnancy and the Puerperium, the Acute Management of (Green-top Guideline No. 37b). 2015.
77. Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AW. Low molecular weight heparin: a critical analysis of clinical trials. Pharmacol Rev. 1994;46(1):89–109.
78. Nurmohamed MT, Rosendaal FR, Buller HR, Dekker E, Hommes DW, Vandenbroucke JP, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet. 1992;340(8812):152–6.
79. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106(2):401–7.
80. Nelson-Piercy C, Powrie R, Borg JY, Rodger M, Talbot DJ, Stinson J, et al. Tinzaparin use in pregnancy: an international, retrospective study of the safety and efficacy profile. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):293–9.
81. Galambosi PJ, Kaaja RJ, Stefanovic V, Ulander VM. Safety of low-molecular-weight heparin during pregnancy: a retrospective controlled cohort study. Eur J Obstet Gynecol Reprod Biol. 2012;163(2):154–9.
82. Mitic G, Kovac M, Povazan L, Djordjevic V, Ilic V, Salatic I, et al. Efficacy and safety of nadroparin and unfractionated heparin for the treatment of venous thromboembolism during pregnancy and puerperium. Srp Arh Celok Lek. 2010;138(Suppl 1):18–22.
83. Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. Prophylaxis with low-dose low-molecular-weight heparin during pregnancy and postpartum: is it effective? J Thromb Haemost. 2011;9(3):473–80.
84. Rodger MA, Hague WM, Kingdom J, Kahn SR, Karovitch A, Sermer M, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet. 2014;384(9955):1673–83.
85. Tengborn L, Bergqvist D. Matzsch T, Bergqvist A, Hedner U. Recurrent thromboembolism in pregnancy and puerperium. Is there a need for thromboprophylaxis? Am J Obstet Gynecol. 1989;160(1):90–4.
86. Gates S, Brocklehurst P, Ayers S. Bowler U, Thromboprophylaxis in Pregnancy Advisory G. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. Am J Obstet Gynecol. 2004;191(4):1296–303.
87. Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. Br J Obstet Gynaecol. 1983;90(12):1124–8.

88. Bleker SM, Buchmuller A, Chauleur C, Ni Ainle F, Donnelly J, Verhamme P, et al. Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomised trial of two doses. Thromb Res. 2016;144:62–8.
89. Scheres LJJ, Bistervels IM, Middeldorp S. Everything the clinician needs to know about evidence-based anticoagulation in pregnancy. Blood Rev. 2019;33:82–97.
90. Cohen H, Arachchillage DR, Middeldorp S, Beyer-Westendorf J, Abdul-Kadir R. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(8):1673–6.
91. Cranenburg EC, Schurgers LJ, Vermeer C. Vitamin K: the coagulation vitamin that became omnipotent. Thromb Haemost. 2007;98(1):120–5.
92. Desborough MJ, Pavord S, Hunt BJ. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH: comment. J Thromb Haemost. 2017;15(1):194–5.
93. Haemostatsis WsHSaSCotISoTa. DOAC in pregnancy registry. https://cdn.ymaws.com/www.isth.org/resource/group/a9f3a2ba-d3e5-4bb6-8b82-508d3c002a06/projects/2015-10-27_SSC_Subcommittee_pdf.
94. Middeldorp S. How I treat pregnancy-related venous thromboembolism. Blood. 2011;118(20):5394–400.
95. Money SR, York JW. Development of oral heparin therapy for prophylaxis and treatment of deep venous thrombosis. Cardiovasc Surg. 2001;9(3):211–8.
96. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014;130(18):1636–61.
97. ten Cate-Hoek AJ, Henke PK, Wakefield TW. The post thrombotic syndrome: ignore it and it will come back to bite you. Blood Rev. 2016;30(2):131–7.
98. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349(9054):759–62.
99. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica. 1997;82(4):423–8.
100. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol. 2009;145(3):286–95.
101. Greer IA. Thrombosis in pregnancy: updates in diagnosis and management. Hematology Am Soc Hematol Educ Program. 2012;2012:203–7.
102. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med. 2008;149(10):698–707.
103. Wik HS, Jacobsen AF, Sandvik L, Sandset PM. Prevalence and predictors for post-thrombotic syndrome 3 to 16 years after pregnancy-related venous thrombosis: a population-based, cross-sectional, case-control study. J Thromb Haemost. 2012;10(5):840–7.
104. Kahn SR, Galanaud JP, Vedantham S, Ginsberg JS. Guidance for the prevention and treatment of the post-thrombotic syndrome. J Thromb Thrombolysis. 2016;41(1):144–53.
105. Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, et al. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. N Engl J Med. 2017;377(23):2240–52.
106. Haig Y, Enden T, Grotta O, Klow NE, Slagsvold CE, Ghanima W, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol. 2016;3(2):e64–71.
107. Ljungqvist M, Holmstrom M, Kieler H, Larfars G. Long-term quality of life and postthrombotic syndrome in women after an episode of venous thromboembolism. Phlebology. 2018;33(4):234–41.
108. Wik HS, Jacobsen AF, Sandvik L, Sandset PM. Long-term impact of pregnancy-related venous thrombosis on quality-of-life, general health and functioning: results of a cross-sectional, case-control study. BMJ Open. 2012;2(6):e002048.
109. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. Lancet Haematol. 2018;5(1):e25–33.
110. Williams-Johnson JA, McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. West Indian Med J. 2010;59(6):612–24.
111. Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ. 2012;345:e4944.
112. Lidegaard O, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ. 2011;343:d6423.
113. Poulter NR, Chang CL, Farley TM, Meirik O. Risk of cardiovascular diseases associated with oral progestagen preparations with therapeutic indications. Lancet. 1999;354(9190):1610.
114. Mannucci PM, Franchini M. The real value of thrombophilia markers in identifying patients at high risk of venous thromboembolism. Expert Rev Hematol. 2014;7(6):757–65.
115. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nat Rev Cardiol. 2014;11(3):140–56.

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APPENDIX

TABLE A1 Evidence-based summary of management strategies for abnormal uterine bleeding during anticoagulant treatment

Management strategy	Evidence for safety in terms of VTE risk	Evidence for efficacy in terms of bleeding prevention	References
Hormonal therapy			
Combined oral contraceptives and anticoagulants (DOAC and VKA)	Risk of recurrent VTE per year: with COC: 3.7%, without COC: 4.7%, adjusted HR 0.6; 95% CI 0.2-1.4).	Not reported	16
Levonorgestrel-releasing IUD	Not reported	PBAC decreased in patients treated with IUD from 239 to 155 points in 6 months	29
Tranexamic acid on demand			
Tranexamic acid on demand	No data on use of tranexamic acid in patients with VTE	No data available	—
	In large robust randomized controlled trials with patients at high risk of VTE, i.e., major trauma, postpartum hemorrhage, orthopedic surgery: no increased VTE risk with tranexamic acid.	40% to 50% reduction in menstrual blood loss in general population	30,33,111
Modification of anticoagulant therapy			
Dose reduction after initial treatment	Recurrent VTE during 1-year follow-up: Rivaroxaban 20 mg: 1.5%, rivaroxaban 10 mg: 1.2%, aspirin: 4.4%	Clinically relevant non-major bleeding during 1 year follow-up: Rivaroxaban 20 mg: 2.7%, rivaroxaban 10 mg: 2.0%, aspirin: 1.8%	EINSTEIN Choice trial [54]
	Recurrent VTE during 1 year follow-up: Apixaban 5 mg: 1.7%, apixaban 2.5 mg: 1.7%, placebo: 8.8%	Clinically relevant non-major bleeding during 1 year follow-up: Apixaban 5 mg: 4.2%, apixaban 2.5 mg: 3%, placebo 2.3%	AMPLIFY-EXT trial [53]
Dose reduction during menses	No data available	No data available	
Switch to alternative anticoagulant	DOACs non-inferior to VKA in treatment of VTE	Occurrence of AUB is lower in VKA treated patients, however no dataavailable whether switching to alternative anticoagulant is beneficial	17,18

Abbreviations: AUB, abnormal uterine blood loss; Ci, confidence interval; COC, combined oral contraceptives; DOAC, direct oral anticoagulant; HR, heart rate; IUD, intrauterine device; PBAC, pictorial blood loss assessment chart; VKA, vitamin K antagonist; VTE, venous thromboembolism.

TABLE A2 Hormonal contraceptive methods and VTE risk

Hormonal contraceptive method	VTE risk (RR, 95% CI), compared with non-users	References
Does not increase VTE risk		
Levonorgestrel-releasing intrauterine device	0.6 (0.2-1.5)	112
Low-dose progestin pill	0.9 (0.6-1.5)	112
Uncertain VTE risk		
Etongestrel birth control implant	1.4 (0.6-3.4)	27
Increases VTE risk		
Combined oral contraceptives		
Ethinylestradiol/levonorgestrel	2.9 (2.2-3.8)	113
Ethinylestradiol/desogestrel	6.6 (5.6-7.8)	113
Ethinylestradiol/drospirenone	6.4 (5.4-7.5)	113
Progestin-only injections (DMPA)	2.7 (1.3-5.5)	112
High dose progestin pills[a]	5.9 (1.2–30.1)	114

Abbreviations: CI, confidence interval; DMPA, depot medroxyprogesterone acetate; RR, risk ratio; VTE, venous thromboembolism.
[a]Generally not used for contraception but for other gynecological indications.

TABLE A3 Estimated absolute VTE risk per 10 000 women per year, for age group 20-24

		Absolute VTE risk per 10 000 women per year, for age group 20-24				
		Baseline risk	Negative family history for VTE		Positive family history for VTE, RR ×2	
Hereditary thrombophilia type	Relative Risk caused by thrombophilia	(without COC)	2nd generation COC, RR ×4	3rd and 4th generation COC, RR ×8	2nd generation COC, RR ×4	3rd and 4th generation COC, RR ×8
General population	1	2	8	16	16	32
Antithrombin deficiency, protein C/S deficiency	4-10	8-20	32-80	64-160	64-160	132-320
Factor V Leiden mutation						
Heterozygous	3-7	6-10	24-40	48-80	48-80	96-160
Homozygous	80	160	640	1280	1280	2560
Prothrombin G20210A mutation						
Heterozygous	2-3	4-6	16-24	32-48	32-48	64-96
Homozygous	5	10	40	80	80	160
Double heterozygosity (Factor V Leiden and prothrombin G20210A)	6	12	48	96	96	192

Notes: These estimates are crude, based on a baseline risk of 2 in 10 000 in young women, known odds ratios for COC of 4 to 8, depending on generation, and relative risk of a positive family history of VTE.[115,116]
Abbreviations: COC, combined oral contraceptives; RR, relative risk.VTE, venous thromboembolism

TABLE A4 Recommendations for antepartum and postpartum thromboprophylaxis for women with thrombophilia but without history of VTE

		Antepartum thromboprophylaxis?		Postpartum thromboprophylaxis?	
Hereditary thrombophilia type	Family history of VTE	ACCP [73]	ASH [74]	ACCP [73]	ASH [74]
Protein C Deficiency	(+)	No	No	Yes	Yes
	(–)	No	No	No	No
Protein S Deficiency	(+)	No	No	Yes	Yes
	(–)	No	No	No	No
Antithrombin deficiency	(+)	**No**	**Yes**	Yes	Yes
	(–)	No	No	No	No
Factor V Leiden mutation, *heterozygous*	(+)	No	No	**Yes**	**No**
	(–)	No	No	No	No
Prothrombin G20210A mutation, *heterozygous*	(+)	No	No	**Yes**	**No**
	(–)	No	No	No	No
Factor V Leiden mutation, *homozygous*	(+)	Yes	Yes	Yes	Yes
	(–)	**No**	**Yes**	Yes	Yes
Prothrombin G20210A mutation, *homozygous*	(+)	**Yes**	***No recommendation***[a]	Yes	Yes
	(–)	No	No	Yes	Yes
Combined thrombophilia	(+)	***No recommendation***	**Yes**	***No recommendation***	**Yes**
	(–)	***No recommendation***	**Yes**	***No recommendation***	**Yes**

Notes: Differences between the recommendations from the ACCP and ASH guidelines in bold.
Abbreviations: ACCP, American College of Chest Physicians; ASH, American Society of Hematology; VTE, venous thromboembolism.
[a]No formal recommendation as no family studies available in homozygous PGM. However, panel members favor antepartum prophylaxis given VTE risk estimates.

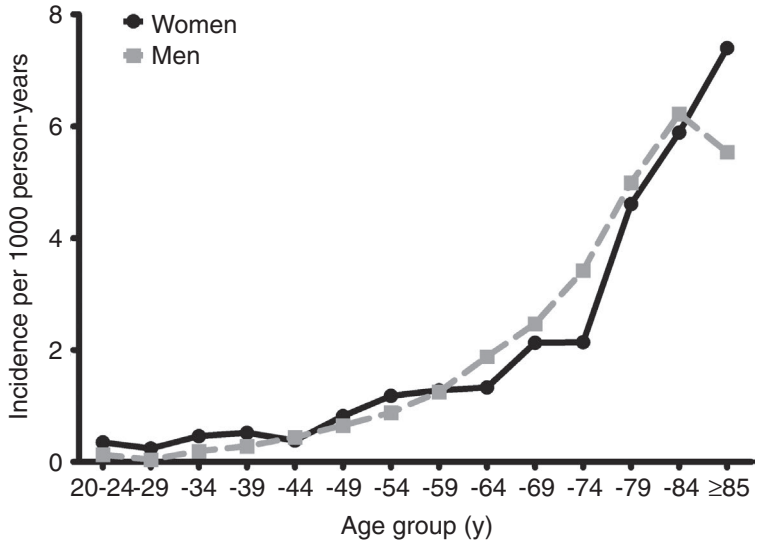

FIGURE A1 Incidence of venous thromboembolism for women (black line) and men (gray, dotted line) separately based on published data by Naess et al[5]

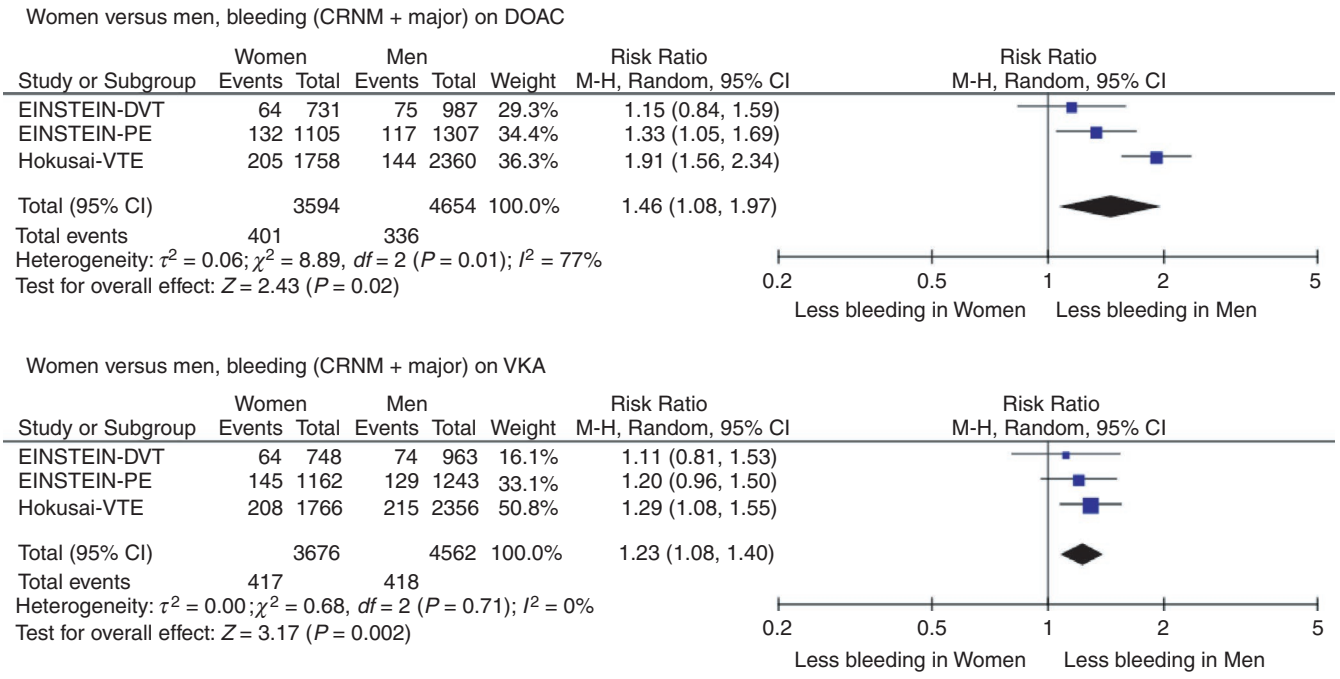

FIGURE A2 Sex-specific differences in risk of composite of major and clinically relevant non-major bleeding