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INVITED REVIEW

Thrombosis in women: what are the knowledge gaps in 2013?

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Summary. Several aspects of the diagnostic and therapeutic management of women with venous thrombosis are uncertain. In this overview, I will discuss three major areas. First, the contribution of hormone use to venous thromboembolism (VTE) will be discussed as prudent prescribing of safe preparations can further reduce the risk of hormone-related VTE. Uncertainties remain regarding certain low-dose progestagens and transdermal routing of hormones and their associated risk of VTE. Second, I will review the diagnosis, treatment, and prevention of pregnancy-related VTE. As direct evidence is largely absent for these individuals, these areas are subject to extrapolation from the non-pregnant population. There is therefore an urgent need for the evaluation of diagnostic strategies that safely exclude the diagnosis of acute pulmonary embolism in pregnant women without the need for diagnostic imaging, which is currently the gold standard, as no studies have confidently demonstrated the safety of ruling out VTE by clinical probability assessment combined with the use of D-dimer levels. Although identification of women at increased risk of pregnancy-related VTE is relatively well established, controversy remains for asymptomatic women from thrombophilic families. The optimal duration and intensity of anticoagulant treatment for, and prophylaxis of, pregnancy-related VTE with low molecular weight heparin is unknown. Third, anticoagulant therapy to prevent recurrence in women with unexplained recurrent miscarriage has shown to have no benefit and should not be prescribed. However, whether antithrombotic therapy prevents recurrent miscarriage in thrombophilic women, or in women with severe pregnancy complications, remains unknown and urgently requires future research.

Keywords: female contraceptive agents, pregnancy complications, pulmonary embolism, thrombophilia, venous thrombosis.

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Introduction

Although Jefferson's immortal phrase that 'all men are created equal' remains true today and includes both men and women having equal human rights, it is clear that important differences between the sexes exist, particularly with respect to the occurrence of cardiovascular diseases, including venous thromboembolism (VTE) [1]. Over the past few decades, increasing attention has focussed on these differences, particularly as many studies on etiology, diagnosis, and treatment have primarily looked at men.

Women and men have similar risks of VTE during their life span, but women are at higher risk during their fertile years, when they are exposed to hormonal risk factors for VTE, for example use of hormonal contraception and pregnancy (Fig. 1) [2,3].

In this review, I will discuss current issues associated with VTE and thrombophilia that are specific to women, with a focus on the gaps that exist in our present understanding that we urgently need to fill in the coming years. I will do so by addressing three specific clinical questions in relation to VTE and thrombophilia that are raised on a daily basis by many women around the world.

Clinical question no. 1: can we safely prescribe female hormones with respect to VTE?

Relevance of hormone use for VTE risk in the general population

Since the introduction of hormonal contraceptives half a century ago, it has been known that the risk of VTE increases during its use [4]. Most of the known risk estimates of VTE associated with hormonal contraceptives are derived from case–control or cohort studies and provide relative risk increases for users compared with non-users [5]. In the interpretation of these relative risks, a valid estimate of the absolute baseline risk of VTE is essential to calculate the absolute risk of VTE by multiplying this baseline risk with the relative risks of VTE associated with hormone use. This indirect estimation of the absolute risk is valuable for clinical practice, although it leads to a modest overestimation of the risk, because the age- and sex-specific baseline risks are derived from

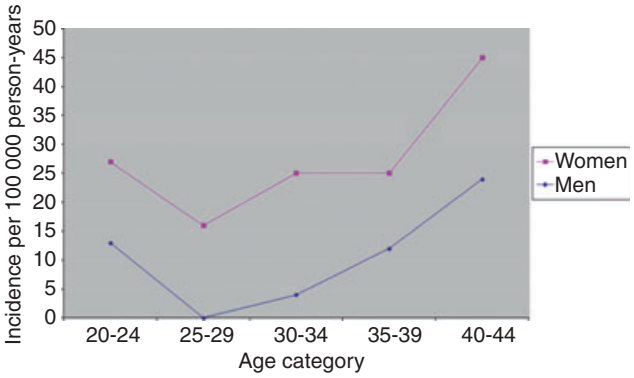

Fig. 1. Incidence of VTE in young women and men. Data derived from the study by Naess *et al.* [3] VTE, venous thromboembolism.

cohorts in which a vast proportion of the women used oral contraceptives. The absolute baseline risk of a first VTE increases sharply with age, in particular after the age of 45 [2,3,6]. The absolute incidence of first VTE in women aged 20–44 was 0.39 per 1000 person-years, increasing to 1.00 per 1000 person-years in women aged 45–54 in a large Norwegian cohort [3]. Therefore, the absolute increase for an individual is very modest for most women and needs to be balanced against the beneficial effects of avoiding unintended pregnancies. However, even a small increase in VTE is relevant due to the large numbers of women using oral contraceptives worldwide, leading to a large population attributable risk and large implications for population health care. Importantly, the relative risk of VTE is the highest in the first three months of use, as was shown in a large case–control study of patients with a first VTE that found an odds ratio of 13 (95% confidence interval [95%CI] 7–22) during the first three months of oral contraceptive use [7]. Of note, despite this 'starters effect', the risk of VTE associated with oral contraceptive use remains approximately 5-fold increased, even after long-term exposure [7], and hence, the contribution of oral contraceptives to the risk of VTE may become more important as a woman's baseline risk rises with age.

It is currently established that hormone replacement therapy (HRT) does not prevent arterial cardiovascular disease and, indeed, even has a detrimental effect during the first year of use [8–10]. However, HRT still is often used to alleviate perimenopausal symptoms or osteoporosis. HRT increases the risk of VTE, and even though the risk increase is smaller than with use of oral contraceptives, the population baseline risk of VTE is higher for older women using HRT than for younger women using hormonal contraception [3,11].

As summarized in Table 1, there are clinically relevant differences in VTE risk increase between various doses and types of estrogen and progestagen, as well as between routes of administration. Therefore, this knowledge should be used by doctors to minimize the contribution of oral contraceptives to VTE in the general female population [7,12]. Table 1 also shows that there remains some uncertainty with regard to the confidence with which we can exclude an increased risk of VTE by the use of specific hormone formulations, for example, for the desogestrel-only progestagen pill (upper limit of the 95%CI 3.4)

Table 1 Overview of differential relative risks of a first VTE for various hormonal contraceptives and HRT

Hormonal contraceptives	Absolute risk (per 1000 person-years)*
Strong risk increase (odds ratio 5–8) [7,105–107]	
Ethinylestradiol†/desogestrel	2.8 (2.1–3.9)
Ethinylestradiol†/cyproterone	2.7 (1.8–3.9)
Ethinylestradiol†/drosperidone	2.5 (1.1–5.3)
Ethinylestradiol†/norgestimate	2.3 (0.7–8.2)
Ethinylestradiol†/gestodene	2.2 (1.4–3.3)
Ethinylestradiol†/lynestrenol	2.2 (1.2–4.0)
Oral progestagen only, high dose (5–30 mg)	2.1 (0.6–7.3)
Moderate risk increase (odds ratio 2–5) [7,108]	
Ethinylestradiol†/noresthisterone‡	1.5 (0.5–4.1)
Ethinylestradiol†/levonorgestrel	1.4 (1.1–1.8)
Injectable depot medroxyprogesterone‡	1.4 (0.7–2.8)
Transdermal ethinylestradiol/ norelgestromin§	1.5 (0.5–4.1)
No risk increase [12,109,110]	
Levonorgestrel releasing IUD	0.1 (0.0–0.4)
Progestagen only, low-dose norethisteron 350 μg or levonorgestrel 30 μg	0.2 (0.1–0.4)
Progestagen only, low-dose desogestrel 75 μg¶	0.2 (0.1–0.7)
Uncertain [111]**	
Etonogestrel subcutaneous implant	0.5 (0.01–2.9)
Vaginal ring (ethinylestradiol/ etonogestrel)	1.5 (0.1–5.4)
HRT	
Moderate risk increase (OR 1.5–3.0) [11,112]	
Oral combined estrogen/progestagen pills	2.6 (2.0–3.2)
Oral estrogen only	2.2 (1.6–3.0)
No risk increase [11,112]	
Transdermal (combined estrogen/progestagen and estrogen only) ††	1.2 (0.9–1.7)
Tibolone	0.9 (0.8–1.1)

HRT, hormone replacement therapy; VTE, venous thromboembolism. *Estimates of the absolute risk were obtained by multiplying the odds ratio with the baseline incidence of VTE of 0.39 per 1000 person-years for women aged 20–44 for hormonal contraceptives, and of 1.00 per 1000 person-years for women aged 45–54 for HRT [3]. †Ethinylestradiol in the most commonly used dose of 30–40 mcg daily. ‡Upper limits of the 95% CIs (10.7 for noresthisterone and 7.1 for injectable depot medroxyprogesterone) do not exclude a strong risk increase. §Inconsistent results from no increased to an increased risk of VTE as compared to oral contraceptives containing norgestimate; no data available of patch users vs. non-users. ¶Upper limit of the 95% CI (3.4) does not exclude a risk increase. **Data from SAE reporting in clinical outcome studies. Wide confidence intervals do not exclude a modest or strong risk increase. ††Upper limit of the 95% CI (1.7) does not exclude a modest risk increase.

and for transdermal HRT patches (upper limit of the 95%CI 1.7).

Hormone use in women at increased risk of VTE

The presence of a hereditary thrombophilia increases the risk of a first episode of VTE in carriers. The relative risk of VTE associated with the use of hormonal contraceptives is similar in women with or without thrombophilia, but due to the higher baseline risk in the former, the absolute risk increase is larger in women with thrombophilia. The baseline risk of VTE in women with thrombophilia depends on the setting in which they were tested. Women with thrombophilia, selected from families with a tendency for VTE, have a higher absolute risk than women with the same defect identified by population testing [13]. Furthermore, individuals with a first-degree relative with VTE have a 2-fold increased risk of VTE, and women with more than one first-degree relative with VTE have a 4-fold increased risk of VTE, regardless of the presence of thrombophilia [14]. For women with inherited thrombophilia and a positive family history of VTE, family cohort studies provide useful estimates of the absolute risk of VTE during oral contraceptive use [15–18]. These risks vary from 0.2% to 0.5% per year for factor (F)V Leiden and the prothrombin 20210A mutation, up to approximately 4% per year for women with antithrombin, protein C, or protein S deficiency. Due to the relatively small number of women using oral contraceptives in these family studies, no distinction between the risks of different types of oral contraception can be made. With these absolute incidences, rough estimates can be calculated of the number of women with thrombophilia that need to refrain from oral contraceptive use to prevent one VTE. For deficiencies of antithrombin, protein C, or protein S, this number is around 50, and for the factor (F)V Leiden and prothrombin 20210A mutations, this number is around 200–400. Finally, approximately 2500 women with a family history of VTE need to refrain from oral contraceptive use in order to prevent one VTE, while this number is approximately 5000 in women from the general population [19,20]. Also, one should bear in mind that replacing oral contraceptives by less reliable contraceptive methods in young women with thrombophilia exposes them to the risk of unintended pregnancies and consequently to an increase in pregnancy-related VTE. We have estimated from family studies that a similar risk of VTE exists with the use of oral contraceptives as with the use of condoms, whereas this is about 3 per 1000 woman-years lower with use of an intra-uterine device (hormone or copper) [21].

Hormone use and the risk of recurrent VTE

Observational data indicate that women who resume oral contraceptive use after VTE have an increased risk of recurrence. In a relatively small follow-up study, women who used an oral contraceptive after VTE had a statistically non-significant 2- to 3-fold increased risk of recurrence, regardless of whether their first VTE was unprovoked or provoked by oral contraceptives [22]. There is some debate whether oral contraceptive use during a (first) VTE, either recently started or after long-term exposure, should be classified as a provoked VTE that would have a lower recurrence rate than an unprovoked VTE. As compared to women with an unprovoked VTE, the relative risk of recurrence in women with a first VTE associated with an oral contraceptive ranges from 0.3 to 1.2 [22–26].

HRT also markedly increases the risk of recurrent VTE. In a double-blind, placebo-controlled randomized controlled trial of HRT in 140 women with prior VTE, the risk of recurrence was 10.7% in the HRT group and 2.3% in the placebo group [27]. This risk may not be increased with the use of transdermal HRT, although the uncertainty about the absence of risk remains due to the relatively small number of patients (HR 1.0, 95%CI 0.4–2.4) [28].

In conclusion, prudent prescribing of hormones in the general population and asymptomatic women at risk should limit the number of hormone-related VTE. After an episode of VTE, combined oral contraceptives or HRT should not be prescribed. Hormone-releasing or copper intra-uterine device is a rational choice, although studies that found no increased VTE were limited to first thrombotic events.

Clinical question no. 2: can we adequately diagnose, treat, and prevent pregnancy-related VTE?

Pulmonary embolism (PE) is a leading cause of maternal mortality in the Western world, and deep vein thrombosis (DVT) in pregnancy is an important cause of short- and long-term maternal morbidity [29–32]. VTE complicates approximately 1–2 of 1000 pregnancies, and the risk increases with age, mode of delivery, and presence of comorbid conditions [29,33,34]. During pregnancy, the risk is increased approximately 5-fold compared with age-matched non-pregnant women, but in the postpartum period, the relative risk has been found as high as 60-fold during the first 3 months after delivery [35]. Approximately two thirds of DVT of the leg occur antepartum and are distributed more or less equally over all trimesters [36]. Given the much longer duration of the antepartum period than the postpartum period, the daily absolute risk of VTE is highest postpartum. The epidemiology of PE appears to differ slightly from DVT, with the majority of pregnancy-related episodes of PE occurring in the postpartum period [33]. Despite these strong risk increases, we lack a strong evidence base for the management of pregnancy-related VTE. Contrary to non-pregnant patients, diagnostic strategies, therapeutic options, and

preventive measures for VTE in pregnant and postpartum women have not been addressed adequately in well-sized observational or intervention studies. Therefore, management is not standardized between physicians, centers, and countries.

Diagnosis of VTE in pregnant women

Studies on the diagnostic and management strategies for DVT and PE have excluded pregnant women, and only a few small studies have addressed the utility of empirical clinical probability assessment or a pregnancy-specific clinical decision rule, with or without the use of D-dimer monitoring [37,38]. Currently, no single study has adequately demonstrated the safety of excluding VTE by clinical probability assessment in combination with the use of D-dimer levels. Hence, for both DVT and PE, objective imaging remains the cornerstone of diagnosis and is crucial if one is to avoid treating the large majority of women with a clinical suspicion of VTE, who do not actually have VTE [39].

Compression ultrasonography (CUS) is an accepted first test in a pregnant patient with a clinical suspicion of DVT. If iliac or pelvic vein thrombosis is suspected because of abdominal, groin, or back pain combined with swelling of the entire leg, a negative CUS needs to be followed by duplex Doppler ultrasound. An absent waveform on modulation of respiration strongly suggests iliac vein thrombosis, but, due to slow flow and external compression by the gravid uterus, false-positive ultrasound results may occur, as well as false-negatives due to nonocclusive thrombi or collaterals. Although in one series, serial CUS testing after an initial normal test demonstrated DVT in four of 152 patients [37], it may be of less value because DVT in pregnancy usually occurs in proximal veins without involvement of the calf veins [40]. In accordance with this, a recent series of 205 women with negative CUS that included assessment of the iliac vein did not find any DVT during serial testing [41].

The optimal diagnostic strategy for PE is debated. Issues requiring attention include radiation risks to fetus and mother, the possibility of false-positive tests, and the long-term risk of cancer. Multi-detector row helical computerized tomography (CT) scanning carries a fetal radiation exposure of approximately 0.013 mSv, compared with 0.026 for single detector row CT, and at least 0.11 mSv for perfusion scintigraphy [42,43]. These fetal radiation exposure rates are much lower than the threshold dose for induction of congenital malformations or malignancies. However, breast tissue receives relatively high doses of radiation during CT pulmonary angiogram (CTPA), which raises concern about the risk of breast cancer attributable to overuse of this diagnostic modality at young age [44]. The diagnostic yield of CUS of the legs is very low in asymptomatic women, and the possibility of a false-positive result should be taken into account, especially if the patient has had an ipsilateral DVT in the past. A recent clinical practice guideline by the American Thoracic Society proposes performing a chest X-ray in all women with suspected PE, followed by perfusion scintigraphy, if normal. If the scintigraphy scan result is nondiagnostic, a CTPA scan should be performed [45]. Perfusion scans were diagnostic in 75%–94% of pregnant women with suspected PE in four studies, with the higher percentages found in women with a normal chest X-ray [46–49]. Hence, in up to a quarter of pregnant patients with suspected PE, perfusion scintigraphy needs to be followed by additional testing, ultimately resulting in a higher amount of fetal radiation exposure. A potential advantage of an algorithm starting with a CTPA scan is the feasibility to reach a diagnostic conclusion combined with a low fetal radiation exposure, although in two previous studies, inconclusive CTPA scans were reported in 19% and 35% of pregnant women [47,50,51]. In a diagnostic management study in which CTPA was used in pregnant women with a clinical suspicion of acute PE, we observed inconclusive results in eight of 142 women (5.6%). (Nijkeuter *et al.,* Abstract # 1612, ISTH 2013) Given the low incidence of PE (< 10% in all contemporary studies) in women with a suspicion, management studies to further increase the *a priori* clinical probability to reduce the number of CTPA or V/Q scans are urgently needed and require international collaborative studies.

Treatment for VTE in pregnancy

Low molecular weight heparin (LMWH) is the preferred choice for treating pregnant women with VTE, because they do not cross the placenta and are safe for the fetus [52]. In the non-pregnant population, the initial use of LMWH for treatment of acute VTE is firmly established and doses are based on body weight, with similar efficacy of once- vs. twice-daily regimens [53]. Also, long-term treatment with LMWH has shown to be at least, and in patients with cancer, more, effective than vitamin K antagonists to prevent recurrent VTE [54,55]. For pregnant patients, several issues remain controversial regarding the use of therapeutic doses of LMWH [56]. These include the uncertainty whether prepregnancy weights can be used to determine the appropriate dose of LMWH, whether monitoring of anti-Xa levels or dose adjustments is required as the pregnancy progresses and body weight increases, and whether a twice-daily regimen should be preferred over a once-daily regimen because the volume of distribution of LMWH changes and glomerular filtration rate increases in the second trimester. Many clinicians use a once-daily regimen to simplify administration and enhance compliance, and prospective observational studies have not demonstrated an increase in the risk of recurrence with the once-daily regimen over the twice-daily regimen [57,58]. The optimal intensity and duration of anticoagulation is an issue that has been addressed

extensively in the non-pregnant population, but not at all in pregnant women. For instance, it is unclear whether a reduction in the therapeutic LMWH dose after the initial 6-week phase, as has been shown to be safe and efficacious in cancer patients with acute VTE [55], further reduces the small risk of bleeding complications in pregnant women [52]. Regarding duration of treatment, a minimum duration of 3 months for proximal VTE is extrapolated from studies in the non-pregnant population [53] and should include the 6-week postpartum period, because the daily risk in any woman to develop VTE is highest during this time [35]. Finally, management of delivery in an anticoagulated woman is an entirely experience-based issue. Several options exist and have been reviewed in detail elsewhere, but the bottom line is that no comparative studies between various strategies have been performed and there is no evidence base to guide decisions [52,56]. Neuraxial anesthesia is contraindicated if therapeutic LMWH has been administered in the previous 24 h [52,59]. In case of an elective delivery, twice-daily therapeutic LMWH should be discontinued 24 h before induction of labor or cesarean section, whereas patients taking once-daily LMWH should use only 50% of their dose on the morning of the day prior to delivery [52,59].

Prevention of pregnancy-related VTE

The optimal approach to prevent pregnancy-related VTE is especially challenging with regard to two issues. First, the identification of women in whom the risks and burden of preventive strategies outweigh the risk of VTE requires good quality observational studies of the natural course of untreated pregnancies in women at risk. Second, the optimal efficacious and safe dose of LMWH, once a decision has been made that prevention is indicated, should be based on randomized intervention studies, preferably using placebo.

In women with a positive family history and/or hereditary thrombophilia who do not have a personal history of VTE, the decision to use pharmacological prophylaxis is based on the absolute risk estimate of having VTE during pregnancy or in the postpartum period. The increase in risk begins early in pregnancy, and, when antepartum prophylaxis is utilized, it should be commenced as early as possible in the first trimester. The threshold to use antepartum prophylaxis is higher given the burden of self-injecting with LMWH over several months as opposed to 6 weeks in the postpartum period. Based on the risk estimates in Table 2, the 9th edition of the ACCP guidelines suggests both antepartum and postpartum prophylaxis in homozygous carriers of the factor (F)V Leiden or prothrombin gene mutations who have a positive family history of VTE [52]. In women with the other inherited thrombophilias who have a family history of VTE, or in homozygous carriers of the factor (F)V Leiden or prothrombin gene mutations without a positive family history of VTE, clinical vigilance antepartum and postpartum prophylaxis with LMWH are suggested [52]. A controversial issue is whether asymptomatic women with a deficiency of a natural anticoagulant (in particular antithrombin deficiency) are at such a high risk that this justifies antepartum prophylaxis. For instance, the reported very high risk of pregnancy-related VTE in women with antithrombin, protein C, or protein S deficiency included many patients who had a history of recurrent VTE, and episodes of VTE were not objectively confirmed [60]. More contemporary family cohort studies in which relatives from patients with VTE and a specific thrombophilia were investigated, showed much lower risks, and were used for the evidence-based guidelines [61].

Women with a history of VTE have a 3- to 4-fold higher risk of VTE during subsequent pregnancies than outside of pregnancy [62]. The absolute risk of recurrent VTE during pregnancy without the use of pharmacological prophylaxis is estimated to be between 2.4% and 10% [63–65]. Data regarding prognostic factors for recurrent VTE during pregnancy, including the presence of provoking risk factors during the first event and hereditary thrombophilia, are inconsistent. Women who had their first episode of VTE provoked by the use of oral contraceptives or related to pregnancy or the postpartum period appear to have a higher risk of recurrent VTE in a subsequent pregnancy than women whose first VTE was unprovoked or associated with a non-hormonal transient risk factor [64–66]. According to the ACCP guidelines, patients can be categorized into groups at low risk (major transient risk factor for VTE), intermediate (hormone or pregnancy-related or unprovoked VTE), or high risk (multiple prior unprovoked VTE or persistent risk factors such as paralysis) during pregnancy. All women with a history of VTE should receive prophylaxis with LMWH for 6 weeks postpartum. For antepartum prophylaxis, the ACCP guidelines suggest to withhold this in women with a low risk of pregnancy-related recurrence (major non-hormonal transient risk factor for VTE) [52]. In women at moderate-to-high risk of recurrence who are not on long-term anticoagulant therapy, prophylaxis with LMWH is recommended during the entire pregnancy. The recommendations are summarized in Table 3. It should be noted that all recommendations on the use of thrombosis prophylaxis to prevent pregnancy-related VTE are based on extrapolation of benefit from other populations, because no adequately randomized intervention studies in pregnant women have been performed.

In women who are on long-term anticoagulant therapy outside of pregnancy, switching to full-adjusted dose LMWH as soon as a urine pregnancy test is positive (i.e. before 6 weeks gestational age) and supply vitamin K 5 mg orally for 3 days is a feasible regimen that I use to minimize the duration of vitamin K deficiency that is known to be able to cause coumadin embryopathy. One

Table 2 Risk of pregnancy-related VTE in thrombophilic women stratified by family history for VTE

Thrombophilic defect	Incidence in population, % [113–117]	Estimated RR OR (95%CI)	Absolute Risk of VTE*, % of pregnancies (95% CI)	
			Family studies	Non-family studies
Factor (F)V Leiden, heterozygous	2.0–7.0	8.3 (5.4–12.7) [84]	3.1 (2.1–4.6) [17,18]	1.2 (0.8–1.8)
Factor (F)V Leiden, homozygous	0.2–0.5	34.4 (9.9–120) [84]	14.0 (6.3–25.8) [118,119]	4.8 (1.4–16.8)
Prothrombin heterozygous	2.0	6.8 (2.5–18.8) [84]	2.6 (0.9–5.6) [15,120]	1.0 (0.3–2.6)
Prothrombin homozygous	Very rare	26.4 (1.2–559) [84]	–	3.7 (0.2–78.3)
Antithrombin deficiency	< 0.1–0.6	4.7 (1.3–17.0) [84]	3.0 (0.08–15.8) [61]	0.7 (0.2–2.4)
Protein C deficiency	0.2–0.3	4.8 (2.2–10.6) [84]	1.7 (0.4–8.9) [61]	0.7 (0.3–1.5)
Protein S deficiency	< 0.1–0.1	3.2 (1.5–6.9) [84]	6.6 (2.2–14.7) [61]	0.5 (0.2–1.0)
Lupus anticoagulants (persistent)†	No consistent data	2–10 (wide CI) [121,122]	–	0.3–1.4 (95%CI uncertain)

VTE, venous thromboembolism. *Observed in family studies, estimated from multiplying the baseline risk of 1.40 per 1000 by the RR in non-family studies [52]. †Risk increase is stronger for lupus anticoagulant than for anticardiolipin or β2 glycoprotein I antibodies. Data are very limited; hence, the estimated absolute risk should be interpreted with caution.

or more days postpartum, women can switch back to their usual anticoagulant therapy while continuing LMWH until the target INR is reached.

Finally, women at increased risk of pregnancy-related VTE are those who have undergone a cesarean section, with a stronger risk increase in emergency settings [34,67]. Again, in the absence of adequate trials in this population, data about the balance of desirable and undesirable consequences of thrombosis prophylaxis and the absolute risk threshold to install prophylaxis need to be extrapolated from general surgery patients. The ACCP guidelines provide an overview of major and minor risk factors to identify women with a high (3%) risk of VTE after cesarean section and suggest using prophylaxis only in these women [52]. The optimal duration of prophylaxis after cesarean section is not established. A commonly used strategy is to continue prophylaxis until discharge from hospital and extend prophylaxis until 6 weeks postpartum in women with ongoing risk factors.

The second main issue in the prevention of pregnancy-related VTE is the optimal dose of LMWH. This dose is controversial, because no evidence from adequate randomized controlled trials is available, and either a prophylactic or an intermediate dose of LMWH to prevent recurrent VTE in pregnancy and the postpartum period is suggested [52]. However, numerous treatment failures have been reported in observational, mainly retrospective studies [64,68,69], with an estimated risk of recurrent VTE despite the use of low-dose LMWH as high as 5%–6% [64,70,71]. However, these studies did not assess compliance and are inconsistent with another study [72]. Potential benefits of the intermediate dose of LMWH consist of superior efficacy as compared to the low dose of LMWH. Harms consist of an increased risk of bleeding, mostly associated with delivery and neuraxial anesthesia, but few data are available. We observed no VTE recurrences in a retrospective study of 95 women who used even therapeutic dose LMWH, whereas the risk of serious postpartum bleeding was not increased compared with 524 women who had delivered in the same hospital without LMWH use [73]. However, another study with a similar design did observe an increased risk of postpartum bleeding over 500 mL after vaginal delivery, without a difference in postpartum bleeds over 1000 mL [74]. It is clear that randomized controlled trials between different doses of LMWH to prevent pregnancy-related VTE are urgently needed.

Clinical question no. 3: can we identify women in whom we can prevent pregnancy complications with antithrombotic agents?

A much debated topic is the role of thrombophilia in, and the potential beneficial effect of antithrombotic agents, for example aspirin or (LMW)H, to prevent, pregnancy complications [75,76]. Pregnancy failure is extremely distressing for couples who desire to have children, and pre-eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) are leading causes of maternal and perinatal mortality and morbidity [77]. Analogous to antiphospholipid syndrome (APS) for which pregnancy failure and pregnancy complications are clinical criteria [78,79], the association between inherited thrombophilic disorders and miscarriage was first detected in family studies of probands, who were identified because of their history of VTE [80–82]. Since then, many

Table 3 Summary of recommendations to prevent a first or recurrent pregnancy-related venous thromboembolism (VTE)*

Antepartum and postpartum prophylaxis	Postpartum prophylaxis during 6 weeks†	No pharmacological prophylaxis†
Women with a single unprovoked episode of VTE, or provoked by use of oral contraceptives, pregnancy, or postpartum	Women with a history of a single episode of VTE related to a major non-hormonal transient risk factor	General population
Women with a history of recurrent VTE	Women with hereditary thrombophilia and a positive family history of VTE‡	Women with a positive family history for VTE‡
Women who are homozygous for factor (F) V Leiden or prothrombin mutation who have a positive family history of VTE‡	Women who are homozygous for factor (F)V Leiden or prothrombin mutation who do not have a positive family history of VTE‡	Women who are heterozygous for factor (F)V Leiden of prothrombin mutation who do not have a positive family history of VTE‡

VTE, venous thromboembolism. *Recommendations are weak, based on a low level of evidence leaving room to individualize prophylactic strategies based on patient's preferences [52]. †Unless women can be categorized into one of the more aggressive prophylactic strategies in this table. ‡A positive family history is defined as having a first-degree relative with VTE.

studies have confirmed the relationship between inherited thrombophilia and pregnancy failure and complications, although this association is modest and varies with type of complication [83–85]. A presumed benefit of antithrombotic therapy, in the absence of perceived harms, has led many clinicians to prescribe LMWH, aspirin, or both to women with placenta-mediated pregnancy complications including recurrent miscarriage, late pregnancy loss and pre-eclampsia, sometimes but not exclusively, based on the presence of thrombophilia. However, the absence of high-quality evidence, even in areas that are not subject to intense debate, for instance in women with APS and recurrent miscarriage, is striking and distressing given the impact of treatment with (LMW)H during the entire pregnancy. Large gaps in evidence result in different recommendations by different scientific communities, as illustrated by the following example. The ACCP guidelines recommend unfractionated heparin or LMWH combined with aspirin for women with APS based on three or more pregnancy losses, but refrain from recommendations for women with APS based on clinical criteria of a single late pregnancy loss, pre-eclampsia, or placental insufficiency [52]. Guidelines of the Royal College of Obstetricians and Gynaecologists state that pregnant women with APS should be considered for treatment with low-dose aspirin combined with heparin to prevent further miscarriage, without mentioning clinical criteria of APS [86]. These recommendations are based on studies with very low numbers of women, and further studies reaffirming this efficacy are warranted [87,88]. However, clinicians worldwide have adopted practice to prescribe antithrombotic agents to all women with obstetric APS. Furthermore, whether the efficacy of heparin combined with aspirin is truly similar when UFH is replaced by LMWH still needs to be determined, as well as the effect of antithrombotic agents in different subgroups of women with APS based on laboratory or clinical criteria, for example women with one late pregnancy loss or severe pre-eclampsia.

For women with an inherited thrombophilia, the subject is heavily debated due to the lack of evidence. The natural history of pregnancy complications without pharmacological treatment is inconsistent in observational studies, and trials without an active intervention arm have not been performed [89–92]. In the SPIN and ALIFE studies (see below paragraph), small proportions of the study populations consisted of women with inherited thrombophilia [93,94]. These subgroup analyses were insufficiently powered to address the effect of antithrombotic treatment in thrombophilic women. In the ALIFE study, a non-significant increase in live birth was observed in the two active treatments arms for women with inherited thrombophilia (relative risk for live birth 1.22 95%CI 0.69–2.16 for aspirin, and 1.31, 95%CI 0.74–2.33 for aspirin combined with nadroparin, as compared to placebo), highlighting the urgent need for new randomized controlled trials. Recently, the ALIFE2 study (www.trialregister.nl, NTR 3361) has started recruiting; a trial in which women with inherited thrombophilia and recurrent pregnancy loss will be randomized to either treatment with LMWH plus standard pregnancy surveillance or standard pregnancy surveillance only.

One clinical trial found promising results in women with a single previous pregnancy loss after 10 weeks' gestation and who had heterozygous factor (F)V Leiden mutation, prothrombin G20210A mutation, or protein S deficiency; they were allocated to enoxaparin 40 mg once daily ($n = 80$) or to aspirin 100 mg ($n = 80$) [95]. Women who were treated with enoxaparin had a much higher chance of a live birth than those allocated to aspirin (86% and 29%, respectively, 57% absolute risk reduction, odds ratio 15.5, 95%CI 7–34). However, several methodological issues were raised, and the results of this single study neither have been confirmed by other trials nor were implemented in the ACCP guidelines [52,96].

The efficacy of antithrombotic agents in women with unexplained recurrent pregnancy loss was compared with no treatment or placebo in two recent randomized trials [93,94]. In the SPIN study, 294 women with two or more unexplained pregnancy losses were randomized to enoxaparin 40 mg combined with aspirin 75 mg plus standard

surveillance or standard surveillance only [93]. No effect of the medical intervention was observed (odds ratio for successful pregnancy 0.91, 95%CI 0.52–1.59). In the ALIFE study, we randomized 364 women with two or more unexplained pregnancy losses to nadroparin 2850 IU combined with aspirin 80 mg, aspirin 80 mg only, or placebo (for aspirin) before conception or at a maximum gestational age of 6 weeks [94]. Of these women, 299 became pregnant. The chance of live birth did not differ between the treatment groups (relative risk of live birth for women who became pregnant was 1.03 (95% CI 0.85–1.25) for nadroparin combined with aspirin, and 0.92 (95% CI 0.75–1.13) for aspirin only, compared with placebo). Based on the updated available evidence that also include trials that compared two active treatments [97], various guidelines recommend against the use of antithrombotic agents in women with unexplained recurrent pregnancy loss [52,86].

Finally, a few trials have investigated the use of LMWH with or without aspirin compared with no treatment in women with a history of various pregnancy complications, including pre-eclampsia, small-for-gestational age babies, and placental abruption, to reduce the risk of recurrence in subsequent pregnancies [98–104]. These studies are relatively small, heterogeneous with regard to type of complications and the inclusion or exclusion of thrombophilia, and results are strikingly positive in some studies with relative risk reductions up to 85% [99–102], whereas in the two most recently published studies in thrombophilic women, no effect on the risk of recurrence of severe pregnancy complications was observed [103,104].

In conclusion, none of the abovementioned intervention studies have clearly and unequivocally shown the benefit of LMWH with or without the addition of aspirin in women with APS, inherited thrombophilia, and recurrent pregnancy loss and women with pre-eclampsia or other severe pregnancy complications. These huge gaps should be filled in the next years by multinational collaborative studies. Acquiring funding and ethical approval for such studies as well as finding patients who are willing to participate may be a hurdle that can only be overcome by mutual scientific enthusiasm and persistence.

Conclusions

Several issues for women with regard to their risk of venous thrombosis remain. First, with respect to hormone use, prudent prescribing of safe preparations can further reduce the risk of hormone-related VTE. Uncertainties are getting smaller but remain with respect to confidence about the absence of a risk increase for certain low-dose progestagens and transdermal routing of hormones. Second, the diagnosis, treatment, and prevention of pregnancy-related VTE are subject to extrapolation from the non-pregnant population and valid observational studies or clinical trial data are scarce or absent. There is an urgent need for the evaluation of diagnostic strategies that safely exclude the diagnosis of acute PE in pregnant women without the need for diagnostic imaging. Although identification of women at increased risk for pregnancy-related VTE is relatively well-established, controversy for asymptomatic women from thrombophilic families still exists. The optimal duration and intensity of anticoagulant treatment for and prophylaxis of pregnancy-related VTE with LMWH is unknown. Third, anticoagulant therapy to prevent recurrence in women with unexplained recurrent miscarriage has shown to have no benefit and should not be prescribed. However, whether antithrombotic therapy prevents recurrent miscarriage in thrombophilic women or in women with severe pregnancy complications is currently unknown and urgently requires future research.

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