Prevention of Venous Thromboembolism during Pregnancy and the Puerperium with a Special Focus on Women with Hereditary Thrombophilia or Prior VTE—Position Paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH)

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Hämostaseologie

Abstract

Venous thromboembolism (VTE) is a major cause of maternal morbidity during pregnancy and the postpartum period. Because there is a lack of adequate study data, management strategies for the prevention of VTE during pregnancy have mainly been deduced from case–control and observational studies and extrapolated from recommendations for non-pregnant patients. The decision for or against pharmacologic thromboprophylaxis must be made on an individual basis weighing the risk of VTE against the risk of adverse side effects such as severe bleeding complications. A comprehensive, multidisciplinary approach is often essential as the clinical scenario is made more complex by the specific obstetric context, especially in the peripartum period. As members of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH), we summarize the evidence from the available literature and aim to establish a more uniform strategy for VTE risk assessment and thromboprophylaxis in pregnancy and the puerperium. In this document, we focus on women with hereditary thrombophilia, prior VTE and the use of anticoagulants that can safely be applied during pregnancy and the lactation period.

Keywords

- venous thromboembolism
- thromboprophylaxis
- pregnancy
- postpartum
- risk assessment
- heparin

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Introduction

Venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the Western world. According to the 2014 systematic analysis by the World Health Organization (WHO), pulmonary embolism (PE) accounted for approximately 14% of maternal deaths in developed countries.[1] During a woman's life, pregnancy and the postpartum period significantly increase the risk of thrombotic events. The risk of VTE in pregnant women is approximately fivefold higher compared with age-matched non-pregnant women.[2–5] The vast majority of these events are venous, with a prevalence of 0.5 to 2.0 per 1,000 pregnant women.[3,6,7] Approximately 75 to 80% of cases of pregnancy-related VTE are caused by deep vein thrombosis (DVT), and 20 to 25% of cases are due to PE.[3] When DVT occurs in pregnancy, it is most often found in the left lower extremity and is more proximal, involving the iliac and iliofemoral veins, compared with that in non-pregnant women.[4,8] During pregnancy, the thrombotic risk is present from the first trimester.[2–4] The VTE risk increases with gestational age and is highest around the time of delivery and immediately postpartum. Approximately one-third of pregnancy-related DVT and half of pregnancy-related PE occur after delivery.[9] A systematic review reported that the risk during the first 6 weeks postpartum was increased 22-fold to 84-fold compared with the risk in non-pregnant women.[10] A recent large, retrospective crossover cohort-study showed that the risk for thrombotic events persists beyond the 6-week postpartum period, although the absolute increase in risk after 6 weeks was low. The odds ratio (OR) for a venous thrombotic event within 6 weeks after delivery was 10.8 compared with 2.2 between 6 and 12 weeks, with no increase beyond 12 weeks postpartum.[11]

Many factors, such as physiologic pregnancy-associated changes in the haemostatic system, functional alteration of venous blood flow and multiple either pre-existing, pregnancy-related or transient risk factors, contribute to the highly thrombotic condition in pregnancy and postpartum (►**Table 1**).[3,5,12–14] The prevalence of VTE in pregnancy and the puerperium and the potentially life-threatening consequences of VTE warrant a VTE risk assessment prior to or in early pregnancy and—when appropriate—the initiation of a medical thromboprophylaxis. However, clinicians have not yet clearly determined the appropriate method to identify those women who are most likely to benefit from thromboprophylaxis during pregnancy or in the postpartum period. No validated risk scores have been published to date. Debate about the optimal strategy to prevent pregnancy-associated VTE also exists. Recommendations from international guidelines on several aspects remain controversial. This position paper has been prepared by an expert panel of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH) to provide assistance in clinical decision making. Recommendations have been developed after conducting a review of the available literature, comparing recommendations from current international guidelines, considering the expertise of the members of the expert panel and reflecting on common clinical practice in German-speaking countries. Informal consensus methods have been used to develop the recommendations listed below, and decisions were finalized by a supermajority (i.e., at least 85% of group members). The expert panel met several times and communicated via telephone conferences and e-mail to discuss controversial issues. After finalization, the position paper was critically reviewed by each author, shared with three external reviewers and endorsed by the members of the GTH executive board prior to publication. The purpose of this paper is to provide assistance in clinical decision making for or against thromboprophylaxis and to establish a more uniform strategy for VTE risk assessment and thromboprophylaxis in pregnancy and the puerperium. In this document, we focus on women with hereditary thrombophilia, prior VTE and the use of anticoagulants that can safely be applied during pregnancy and the lactation period. For the diagnosis and treatment of pregnancy-associated VTE, we refer to recently published articles from our working group.[15,16]

Pregnancy-Associated Physiological Changes

Pregnancy is associated with physiologic and anatomic changes that increase the risk of thromboembolism. Normal pregnancy is characterized by changes in the blood composition that result in a hypercoagulable state. There is a marked increase in procoagulant activity, manifested by an elevation of coagulation factors VII, VIII, X, fibrinogen and von Willebrand factor and a profound decrease in physiologic anticoagulants, manifested mainly by a reduction of free protein S (PS). Acquired resistance to activated protein C (PC) is found in as many as 40 to 60% of pregnancies, increases in the second and third trimesters and depends on the laboratory test system.[17,18] In addition, the overall fibrinolytic activity is impaired during pregnancy.[19,20] Of note, the activities of PC and antithrombin (AT) appear to be unaffected by gestation. Additionally, there is an increase in venous stasis of the lower extremities due to progesterone-induced venous dilatation and due to mechanical compression of the inferior vena cava and pelvic veins by the enlarging uterus. Endothelial injury occurs in preeclampsia and may also result from delivery-related trauma.

Individual Risk Factors for VTE

In addition to these pathophysiological pregnancy-related changes, there are multiple other risk factors (pre-existing, transient and pregnancy-related) that increase the risk of VTE.

Personal History of VTE

The most important individual risk factor for VTE in pregnancy is a *personal history of DVT and/or PE*. Women with a history of VTE have a threefold to fourfold higher risk of VTE recurrence during pregnancy than outside pregnancy.[21] The absolute risk of recurrent VTE during pregnancy without the use of pharmacological prophylaxis was 2.5% in a large prospective study that investigated 125 pregnant women with a single previous

Table 1 Risk factors for VTE in pregnancy

Pre-existing risk factors	aOR (95% CI)	Pregnancy-related risk factors	aOR (95% CI)	Transient risk factors	aOR (95% CI)
Previous VTE	24.8 (17.1–36)	Multiple pregnancy	2.7 (1.6–4.5)	Hyperemesis	2.5 (2–3.2)
Known thrombophilia	[a]	Weight gain > 21 kg	1.6 (1.1–2.6)	Assisted reproductive technique	2.7 (2.1–3.6)
Age > 35	1.5 (1.1–2.2)	Preeclampsia	3.1 (1.8–5.3)	Ovarian hyperstimulation syndrome	87.3 (54.1–140.8)
Obesity (BMI ≥ 30 kg/m^2)	4.4 (3.4–5.7)	Stillbirth	6.2 (2.8–14.1)	Antepartum immobilization (strict bed risk > 1 wk) with pre-pregnancy BMI ≥ 25 kg/m^2 pre-pregnancy BMI < 25 kg/m^2	62.3 (11.5–337) 7.7 (3.2–19)
Smoking (10–30 cigarettes/d prior to or during pregnancy)	2.1 (1.3–3.4)	Preterm delivery < 37 wk	2.7 (2–6.6)		
Parity ≥ 3	1.0 (0.6–1.8)	Caesarean section	2.1 (1.8–2.4)		
Anaemia	2.6 (2.2–2.9)	Peripartum haemorrhage (> 1 L)	4.1 (2.3–7.3)		
Varicosis	2.69 (1.53–4.7)	Postpartum infection	4.1 (2.9–5.7)		
Family history of VTE (any relative)	2.2 (1.9–2.6)	Transfusion	7.6 (6.2–9.4)		
Comorbidities: e.g.					
Heart disease	7.1 (6.2–8.3)				
Sickle cell anaemia	6.7 (4.4–10.1)				
Systemic lupus erythematosus	8.7 (5.8–13)				
Active inflammatory bowel disease	3.46 (1.1–10.7)				
Diabetes mellitus	4.1 (2.0–8.9)				

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; VTE, venous thromboembolism; L, liter; wk, week.
Notes: Besides pathophysiological pregnancy-related changes, there are multiple risk factors that increase the risk of VTE in pregnancy. The most important individual risk factor is a personal history of VTE and a known thrombophilia.[3,5,12–14]
[a]Depending on the thrombophilic defect (see ►**Table 2**).

episode of a VTE.[22] Of note, the risk may be underestimated because the duration of pregnancy at enrolment was 15 ± 6 weeks. In two large retrospective cohort studies, the absolute risk of VTE recurrence in the antepartum period of women with previous VTE without pharmacological prophylaxis was between 5.8 and 10.9%.[21,23] The risk of recurrence depends on the circumstances under which the first VTE occurred. In a cohort study including 1,104 pregnant women with a prior VTE, the rate of recurrence was 7.5% if the first VTE was unprovoked or related to pregnancy or to oral contraceptive (OC) use.[23] Women who had their first episode of VTE related to a high estrogen state (e.g., provoked by use of OC 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 related to a non-hormonal transient risk situation (e.g., trauma, surgery, immobility).[21,23,24]

Hereditary Thrombophilia and Family History of VTE

At least one heritable *thrombophilia* is found in 20 to 50% of pregnancy-related VTEs.[25,26] The risk of VTE is increased in pregnant women with known inherited thrombophilia and is substantially higher in those with multiple thrombophilic defects.[25] Of note, the number of studies investigating the

Table 2 Inherited thrombophilias and VTE risk during pregnancy[27]

Thrombophilic defect	Incidence in general population	Estimated RR in pregnancy OR (95% CI)	Absolute risk of VTE,[a] % of pregnancies (95% CI)	
			Studies with positive family history	Non-family studies
FVL, heterozygous	2.0–7.0	8.3 (5.4–12.7)	3.1 (2.1–4.6)	1.2 (0.8–1.8)
FVL, homozygous	0.2–0.5	34.4 (9.9–120)	14.0 (6.3–25.8)	4.8 (1.4–16.8)
PGM, heterozygous	2.0	6.8 (2.5–18.8)	2.6 (0.9–5.6)	1.0 (0.3–2.6)
PGM, homozygous	Very rare	26.4 (1.2–559)	–	3.7 (0.2–78.3)
Antithrombin deficiency[b]	<0.1–0.6	4.7 (1.3–17)	3.0 (0.08–15.8)	0.7 (0.2–2.4)
Protein C deficiency	0.2–0.3	4.8 (2.2–10.6)	1.7 (0.4–8.9)	0.7 (0.3–1.5)
Protein S deficiency	<0.1–0.1	3.2 (1.5–6.9)	6.6 (2.2–14.7)	0.5 (0.2–1.0)

Abbreviations: CI, confidence interval; FVL, factor V Leiden mutation; PGM, prothrombin 20210 gene mutation; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.
[a]Observed in family studies, estimated from multiplying the baseline risk of 0.14% pregnancies by the RR in non-family studies.
[b]VTE risk in AT-deficient pregnant women can increase up to ≈50-fold, depending on the type and extent of antithrombin deficiency.[26]

association of thrombophilia and the risk of VTE during pregnancy and the postpartum period is low, and risk estimates vary significantly according to study design and the presence of additional risk factors such as a positive family history (►**Table 2**).[27] The most common hereditary thrombophilias that predispose to VTE in the European population are the heterozygous forms of the factor V Leiden (FVL; c.1691G > A, rs6025) and prothrombin G20210A mutation (PGM; c.20210G > A, rs1799963), which are present in approximately 5 and 2% of healthy subjects, respectively.[28] The prevalence of FVL or PGM in women with a history of VTE during pregnancy and puerperium is much higher and has been reported to be approximately 28 and 8%, respectively.[26] However, women who are heterozygous for FVL or PGM and have no additional risk factors are considered to have a low risk of VTE in the antepartum and postpartum period (absolute risk ≈ 1%).[26,29] Pregnant women with homozygous or combined heterozygous FVL and PGM are at especially higher VTE risk with an increase of the absolute risk up to 4 to 14%.[30] In general, women with a PC and PS deficiency and no prior and family history of VTE seem to have a risk for VTE of <1% in the antepartum and postpartum periods.[31] The risk of the rare AT deficiency is difficult to predict and varies according to the subtype of deficiency. Individuals with quantitative defects (type I) or reactive site or pleiotropic mutations (types IIa and IIc) display a significantly increased risk of VTE compared with individuals with mutations of the heparin-binding site (type IIb). Because deficiencies of the physiologic coagulation inhibitors AT, PC and PS are rare in the general population and therefore also among pregnant women, risk estimates are uncertain. Most studies have analysed only a small number of cases or were cohort studies including family members. The risk increases with the degree of reduced activity levels and with the specific underlying mutation.[26] Considering the risk of VTE, we define severe deficiencies of the natural coagulation inhibitors AT, PC and PS, as well as homozygosity for FVL or PGM or combined heterozygosity for FVL and PGM, as "high-risk" thrombophilia, whereas heterozygosity for FVL or PGM is considered "low-risk" thrombophilia.

Further, the individual thrombotic risk in a pregnant woman with a heritable thrombophilia is augmented by the presence of a *positive family history* of VTE, especially in first-degree relatives.[32] A positive family history increases the risk for VTE two to fourfold. Data showing a positive family history, as presented in ►**Table 2**, must be interpreted with caution because the definition of family history varies according to each study.

Acquired Thrombophilia

Anti-phospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia. It is characterized by the presence of anti-phospholipid (APL) antibodies that are directed against phospholipid-binding plasma proteins, such as β-2-glycoprotein I (b2GPI). Its main manifestations are recurrent vascular thromboses (so-called "thrombotic APS") and pregnancy complications ("obstetric APS"). The risk of venous and arterial thromboembolism and pregnancy morbidity increases with the number of positive APL tests and the magnitude of antibody titres, and it is particularly increased in pregnant women with triple positivity for APL (i.e., lupus anticoagulant, anti-cardiolipin immunoglobulin G [IgG] or IgM and anti-b2GPI IgG or IgM positivity).[33,34] For specific recommendations concerning the management of pregnant women with APS or APL, we refer to a recently published review article by Garcia and Erkan.[35]

Additional Risk Factors for VTE

Obesity is a risk factor for VTE in pregnancy.[3,36–38] In a population-based nested case–control study, Larsen et al showed that the adjusted OR for obesity with a body mass index (BMI) > 30 kg/m^2 was 9.7 (95% confidence interval [CI]: 3.1–30.8), during pregnancy and 2.8 (95% CI: 0.8–9.8) in the postpartum period, respectively.[36] Antepartum *immobilization*, which is defined as strict bed rest for 7 days or more during pregnancy, has been identified as a strong risk

factor for both antepartal and postpartal VTE.[13] A multiplicative effect of immobilization and obesity on VTE risk has been observed in women with an increased BMI.[13] Further on, the risk of VTE in pregnant women is increased during admissions to the hospital that are not related to delivery (relative risk: 17.5; 95%CI: 7.7–40.0) and has been shown to remain significantly higher in the 28 days after discharge.[39]

The risk of VTE after *assisted reproductive technologies* (ARTs) is increased ≈twofold compared with the background pregnant population.[12] However, the absolute risk remains low and has been estimated to be 0.1 to 0.3% per cycle of in vitro fertilization.[40,41] The majority of thromboembolic events after ART occur in women with ovarian hyperstimulation syndrome (OHSS). In women with severe *OHSS*, the absolute risk of VTE increases to 1 to 4%. Of note, OHSS patients are particularly at risk for jugular vein and upper-extremity DVT.[42,43]*Delivery by caesarean section* increases the risk for VTE approximately two- to fourfold when compared with vaginal delivery.[3,44,45] The pooled incidence rate was found to be 2.6 per 1,000 caesarean deliveries and was especially increased when the caesarean section was performed as an emergency.[46] Concomitant infections and major postpartum haemorrhage also increase the risk of VTE in women after delivery by caesarean section. Among healthy pregnant women undergoing an elective caesarean section, VTE risk is low.[47]

VTE Risk Assessment and Evaluation for Antithrombotic Prophylaxis

Because VTE is one of the leading causes of maternal mortality, all women should be evaluated for VTE risk in early pregnancy or pre-pregnancy. In this context, special consideration should be given to women with prior VTE, known thrombophilia and/or a family history of VTE.[48]

If testing for thrombophilia is considered, it should preferably be performed before pregnancy. Physiological changes of coagulation factors complicate the interpretation of test results during pregnancy and the early postpartum period. PS, for example, decreases early in pregnancy, and subnormal levels of PS can be detected as early as the first trimester.[49] In addition, resistance to activated PC is found in approximately 40 to 60% of pregnancies.[17,18] In general, thrombophilia testing in pregnancy cannot be recommended and should only be performed if treatment decisions would be influenced by the test results.

Many other factors contribute to the risk of VTE, and the risk increase is even more pronounced if several risk factors are present. Complications during pregnancy or at the time of delivery can further increase the VTE risk. Therefore, risk assessment should be repeated if a woman is admitted to the hospital or develops intercurrent problems necessitating prolonged immobility or hospitalization. VTE risk assessment should also be repeated after delivery, especially after caesarean section.

There is consensus between current international guidelines that thromboprophylaxis should be individualized according to patient risk factors. However, apart from women with a prior VTE, where relatively clear recommendations for medical thromboprophylaxis from current guidelines exist,[40,41,50–52] it remains unknown whether different VTE risk factors must be considered in an additive or multiplicative way, and available evidence does not allow an accurate risk estimation of VTE. Thus, recommendations for risk stratification vary among current guidelines. For example, according to the Society of Obstetricians and Gynaecologists of Canada (SOGC 2014), pharmacologic thromboprophylaxis is recommended if the estimated absolute risk of one or multiple risk factors is greater than 1%.[41] In contrast, the latest guideline of the 'Royal College of Obstetricians and Gynaecologists' (RCOG 2015) recommends risk stratification for thromboprophylaxis on the basis of a special risk scoring system weighting individual risk factors between one point (low risk) to a maximum of 4 points (very high risk).[51] Finally, the latest guideline from the 'American Society of Hematology' (ASH 2018) is based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and to formulate recommendations.[50]

In addition to the understanding of possible risk factors, the prevention of thrombotic events requires the proper use of thromboprophylaxis medication and an ongoing risk assessment during pregnancy and the puerperium. A Cochrane systematic review of thromboprophylaxis during pregnancy and the early postpartum period, analysing 16 randomized controlled studies including 2,592 women, stated that current data are insufficient to make precise recommendations for thromboprophylaxis.[53] Recommendations regarding the use of thromboprophylaxis to prevent pregnancy-related VTE are therefore mainly based on small observational trials and indirect evidence about the relative effects of thromboprophylaxis from non-pregnant patient populations. Of note, current international guidelines are ambiguous with regard to indication, duration and intensity of pharmacologic thromboprophylaxis. When considering pharmacologic thromboprophylaxis during pregnancy, it is important to weigh the benefits against the risks of antithrombotic medication. Because heparins do not cross the placenta, they are the anticoagulants of choice during pregnancy. However, there are side effects to consider, such as pain and bruising at injection sites, allergic skin reactions, heparin-induced thrombocytopenia (HIT) and heparin-induced osteoporosis, when administered over a long time. Among these side effects, bleeding complications are considered the most important adverse outcome of antithrombotic therapy. Unfortunately, data are not sufficient to determine the risk of fatal bleeding in women receiving low-molecular-weight heparins (LMWHs) during pregnancy. In studies of non-pregnant patients with prophylactic or therapeutic anticoagulation, the proportion of fatal bleedings was two to threetimes higher than the proportion of fatal VTEs.[54,55] In contrast, a systematic review reported a case fatality rate for pregnancy-associated VTE of 0.7%.[56]

Therefore, it has been argued that pharmacologic prophylaxis has to prevent at least two to three more VTE events to be considered safe and beneficial[31].

In a meta-analysis conducted in 2005 on LWMH safety including 64 studies and 2,777 pregnancies, Greer and Nelson-Piercy reported the risk for severe antepartum bleeding of 0.4% and for severe postpartum bleeding of 0.9%.[57] In a 2013 systemic review, Romualdi et al analysed data from 941 pregnant women treated with therapeutic doses of LWMH (84%) or unfractionated heparin (UFH; 16%) for acute VTE.[58] The authors reported that the incidence of major bleeding was 1.4% antepartum and 1.9% during the first 24 hours after delivery. Thus, if pharmacologic thromboprophylaxis is considered during pregnancy or the puerperium, the risk of VTE must be substantially higher than the risk of severe bleeding complications due to anticoagulant therapy. These considerations have been adopted by some guidelines and expert panels and resulted in recommendations that the absolute risk of VTE has to exceed 1 to 5% before pharmacologic prophylaxis is beneficial for the woman.[41,59]

In clinical practice, the most common reasons women are considered for thromboprophylaxis are prior VTE, known thrombophilia or a family history of VTE. Therefore, the following sections will focus on these situations and provide advice for decisionmaking for or against pharmacologic thromboprophylaxis. Notably, the woman's values and preferences should be prioritized, given the lack of data from appropriate studies and the weaknesses of many recommendations.[60,61]

- *Recommendation 1*: An individual assessment for VTE risk should be performed in all women prior to pregnancy and repeated when pregnancy is achieved and before and after delivery. In addition, VTE risk should be reassessed on admission to hospital and when additional clinical problems occur (e.g., prolonged immobilization).
- *Recommendation 2*: Pregnant women at an increased risk of VTE should be informed about the symptoms and signs of DVT and PE and instructed to immediately visit their physician or an emergency department to confirm or exclude the diagnosis of VTE.
- *Recommendation 3*: The decision to offer thromboprophylaxis should be based on a woman's absolute risk of VTE during pregnancy and the puerperium and must also consider the absolute bleeding risk of pharmacologic thromboprophylaxis and individual preferences.

Prevention of Pregnancy-Related VTE in Women with Known Thrombophilia

The evidence on which to base guidance on the prevention of VTE in pregnant women with known thrombophilia and without prior VTE is limited. Absolute risk estimates for the different hereditary thrombophilic defects determined from family and non-family studies are provided in ►Table 2. An overview of current recommendations from international guidelines is shown in ►Table 3. According to the aforementioned assumptions that the absolute risk of VTE has to exceed 1 to 5% before a benefit of thromboprophylaxis can be expected, and taking current international guideline recommendations into account, we suggest pharmacologic thromboprophylaxis during pregnancy and in the postpartum period thefollowing.

- *Recommendation 4*: In women with known thrombophilia and without prior VTE, the decision of pharmacologic thromboprophylaxis should be made based on the underlying thrombophilic defect, considering a positive family history of VTE as well as additional VTE risk factors and the woman's preference. If antepartum thromboprophylaxis is considered, it should preferentially be initiated during the first trimester and should be continued for at least 6 weeks postpartum.

Heterozygous FVL or Heterozygous PGM

The risk of VTE in pregnant women without prior VTE who are heterozygous for FVL or PGM is low (≈1%). The risk increases up to ≈3% in heterozygous carriers of FVL or PGM with a positive family history of VTE. Current guidelines do not generally recommend pharmacological thromboprophylaxis for these asymptomatic women during pregnancy.[40,41,50–52] Some guidelines recommend that clinicians consider antepartum thromboprophylaxis if a positive family history or additional risk factors (e.g., immobilization for ≥7 days due to comorbidities) are present.[41,51,52] Additionally, the RCOG guideline stratifies VTE risk according to the number of additional risk factors and the phase of pregnancy (before or after 28 weeks of gestation).[51] Due to the higher risk of VTE in the postpartum period, a tendency to recommend pharmacological prophylaxis in the 6-week postpartum period exists, particularly in women with a positive family history.[40,41,51,52] The ASH guideline published in 2018 is the only one to argue against antepartum or postpartum thromboprophylaxis for women without a prior VTE, regardless of the family history.[50]

Homozygous or Compound Heterozygous FVL and PGM

Women with homozygous or compound heterozygous forms of FVL and PGM have a substantially higher risk of pregnancy-associated VTE (absolute risk ≈4–14%), and therefore, pharmacologic thromboprophylaxis for 6 weeks postpartum has been recommended.[40,41,50,52] Additional antepartum thromboprophylaxis is advocated by several international guidelines[40,41,50–52] and should cover the whole pregnancy, especially in cases of a positive family history or additional VTE risk factors. In contrast, the 2012 version of the 'American College of Chest Physicians' (ACCP) guideline recommends clinical vigilance as the management strategy of choice and advices pharmacologic thromboprophylaxis only for those women who exhibit additional risk factors or a positive family history.[40] Clinical vigilance means that the pregnant woman and her physicians are alert to potential risk factors and situations and to the signs and symptoms of VTE. However, because the two gene mutations derive from different family members that most likely have only a heterozygous mutation, the impact of a negative family history is difficult to consider.

- *Recommendation 5*: For pregnant women with a low risk of thrombophilia, i.e., heterozygous for FVL or PGM, no prior VTE and no additional risk factors, we do not recommend antepartum pharmacological thromboprophylaxis. Because

Table 3 International guideline recommendations for thromboprophylaxis in women with thrombophilia

History	Presence and risk category for thrombophilia[a]	Risk period: antepartum (AP) vs. postpartum (PP)	ACCP, 2012[40]	SOGC, 2014[41]	RCOG, 2015[51]	ACOG, 2018[52]	ASH, 2018[50]	GTH, 2019
No personal history of VTE, No family history of VTE	No	AP	–	–	–	–	–	–
		PP	–	–	–	–	–	–
	Yes: low risk	AP	–	+/–	+/–	–	–	+/–
		PP	–	+/–	+/–	+/–	–	+/–
	Yes: high risk	AP	–	+	+	+	[b]	+
		PP	+	+	+	+	[c]	+
No personal history of VTE, Positive family history of VTE	No	AP	–	–	–	–	–	–
		PP	–	–	–	–	–	–
	Yes: low risk	AP	–	+/–	+/–	+/–	–	+/–
		PP	+	+/–	+	+	[c]	+
	Yes: high risk	AP	+	+	+	+	[b]	+
		PP	+	+	+	+	[c]	+

Abbreviations: ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians and Gynecologists; ASH, American Society of Hematology; GTH, The Working Group in Women's Health of the Society of Thrombosis and Haemostasis; RCOG, Royal College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, venous thromboembolism.
Note: +/–, May consider thromboprophylaxis based on the presence and number of other VTE risk factors.
[a]Definitions of low- versus high-risk thrombophilias differ in the guidelines. Factor V Leiden (FVL) and prothrombin gene mutation heterozygosity are considered low risk by all six organizations. Homozygosity or compound heterozygosity for FVL and prothrombin gene mutation are considered high risk by all six organizations. Protein C or S deficiency is considered high risk only by RCOG and GTH in the case of severe deficiency (PC activity < 50%, PS activity < 40%). Antithrombin deficiency is considered high risk by ACOG, RCOG, SCOG and GTH in the case of severe deficiency (AT activity < 60%).
[b]Prophylaxis is only suggested for women who are homozygous for the FVL mutation or who have combined thrombophilias and for women with antithrombin deficiency who have a positive family history.
[c]ASH guideline recommends postpartum antithrombotic prophylaxis in women with a family history of VTE who have antithrombin deficiency and suggests medical prophylaxis in women with a family history of VTE who have protein C or S deficiency. For women with combined thrombophilias or who are homozygous for the FVL or PG mutation, regardless of family history, the ASH guideline suggests postpartum antithrombotic prophylaxis.

the risk of VTE remains low in the postpartum period, we do not generally recommend pharmacological prophylaxis in the postpartum period either. The decision to administer antepartum and/or postpartum thromboprophylaxis should depend on whether a positive family or additional VTE risk factors are present. For patients with a significantly increased risk, we recommend LWMH with a prophylactic dose regimen. Because of a substantially higher VTE risk in pregnant women who are homozygous or compound heterozygous for FVL and PGM, we recommend antepartum and postpartum thromboprophylaxis for these patients.

Deficiencies of Protein C, Protein S or Antithrombin

The risk of VTE in pregnant women with a PC, PS or AT deficiency without prior VTE and no family history for VTE seems to be low (<1%). Thus, thromboprophylaxis during pregnancy is not generally recommended in current guidelines. The most recent ACCP and ASH guidelines consider hereditary deficiencies in PC or PS as minor risk factors for pregnancy-related VTE and recommend antepartum and postpartum clinical vigilance rather than pharmacological thromboprophylaxis for women with no prior VTE and no family history of VTE.[40,50] Because the VTE risk is substantially higher in women with a positive family history of VTE, current guidelines consistently recommend pharmacological prophylaxis for the 6-week postpartum period.[40,41,50–52]

However, risk estimates vary strongly based on the underlying mutation.[40,62–64] In observational studies of non-pregnant patients, a dose–response effect has been demonstrated insofar that decreasing activity levels of AT, PC or PS are associated with an increasing risk of VTE.[65,66] Thus, a substantial reduction in activity levels (e.g., AT < 60%, PC < 50% and free PS < 40%) is associated with a substantial increase in the VTE risk.[26,31] It is important to note that PS activity levels decrease physiologically with ongoing pregnancy, so that a reliable diagnosis of PS deficiency during pregnancy is not possible. PS testing should therefore be performed outside of pregnancy and at the earliest 8 to 12 weeks after delivery. Even outside of pregnancy there are many causes of acquired PS deficiency that must be considered, and special attention has to be paid to avoid pre-analytical errors.[67] Because patients with AT deficiency are supposed to be at higher risk of VTE than patients with PC or PS deficiency, some guidelines advocate antepartum and postpartum thromboprophylaxis for AT-deficient women.[41,51,52] It is important to note that heparins exert their activity by binding to AT. Because their anticoagulant effect may be attenuated in AT-deficient women, monitoring of anti-factor-Xa levels is recommended, and LMWH dose adjustment

may be required.[16,68] For a detailed description of the management of hereditary AT deficiency in pregnancy and at term, we refer to a recent comprehensive review.[69]

- *Recommendation 6*: The risk of VTE in pregnant women with one of the rare inhibitor deficiencies (i.e., AT, PC or PS) is difficult to predict. In patients with a severe reduction of activity levels, a positive family history or additional VTE risk factors, we recommend pharmacological prophylaxis for 6 weeks postpartum. If the risk of VTE is also considered to be high throughout pregnancy, thromboprophylaxis covering the whole duration of pregnancy should be considered. For those receiving pharmacologic thromboprophylaxis, we recommend prophylactic-dose LMWH. Given the lack of reliable data, the decision for or against thromboprophylaxis should be estimated on an individual basis taking into account additional VTE risk factors and individual preferences. Women with one of the rare inhibitor deficiencies should be counselled at specialized centres for coagulation disorders or vascular medicine.

Prevention of VTE in Pregnant Women with Other Risk Factors

Due to a lack of evidence concerning the benefits of antithrombotic therapy during pregnancy, pharmacologic thromboprophylaxis for isolated pregnancy-related VTE risk factors cannot be recommended. Isolated pregnancy-related risk factors other than thrombophilia generally do not increase the absolute risk of VTE greater than 1%.[13,39] However, thromboprophylaxis should be considered in women with a BMI $\geq 30\ kg/m^2$ or multiple risk factors and prolonged immobilization (i.e., ≥ 7 days).[13] Temporary thromboprophylaxis should also be considered in women with hyperemesis gravidarum, especially if admitted to the hospital, and in women requiring non-obstetrical surgery during pregnancy.[41,51] Routine thromboprophylaxis is not recommended for pregnancies induced by ART, but it can be considered for women with additional VTE risk factors. If severe OHSS occurs, temporary thromboprophylaxis with prophylactic-dose LMWH up to 3 months after resolution of symptoms should be considered.

Prevention of Recurrent VTE in Pregnant Women with Prior VTE

Due to the higher VTE risk in pregnant women with prior VTE, all women with a previous VTE should be offered pre-pregnancy counselling, and a prospective management plan for thromboprophylaxis during pregnancy and the puerperium should be established.[51] According to current ACCP guidelines, women can be categorized into three groups: women are at *low risk* if the prior VTE was provoked by a major transient risk factor (e.g., trauma, surgery, immobility); at *intermediate risk* if the VTE occurred in a previous pregnancy, the puerperium, in the context of OC intake or if the VTE was unprovoked; and at *high risk* due to multiple unprovoked VTE or persistent risk factors, such as paralysis.[40] Regardless, the performance of a baseline compression ultrasound of the previously affected leg prior to or early in pregnancy can be useful to determine the extent of residual thrombus material and post-thrombotic changes. This approach is helpful for the differentiation of residual thrombosis from new disease in women presenting with symptoms of a DVT during pregnancy or postpartum.[40]

Women with Prior VTE No Longer on Anticoagulant Therapy

According to the aforementioned risk stratification, the ACCP guideline recommends thromboprophylaxis with LMWH during the entire pregnancy and for 6 weeks postpartum for women at an intermediate or high risk of VTE recurrence who are no longer on anticoagulation therapy.[40] This recommendation is basically consistent with the recommendations of other international guidelines.[41,50–52] In these cases, LMWH is generally initiated in the first trimester after pregnancy is confirmed. In patients with a *low risk* of recurrence (i.e., provoked VTE related to a major transient risk factor and unrelated to hormonal treatment or pregnancy), clinical surveillance during pregnancy is generally preferred over pharmacological thromboprophylaxis.[40] Notably, the RCOG guideline recommends that clinicians withhold thromboprophylaxis until the 28th week of gestation and initiate antepartum pharmacological thromboprophylaxis in the third trimester.[51] In each case, thromboprophylaxis should be individualized according to the woman's and pregnancy-related risk factors. Attention should be paid to women with known thrombophilia. Medical thromboprophylaxis is recommended in risk situations, and timely and appropriate investigations should be performed in women upon the occurrence of symptoms suspicious of DVT or PE. As the average daily risk is higher in the postpartum period compared with the antepartum period, it is advocated that all women with a history of VTE should receive prophylaxis with LMWH for at least 6 weeks postpartum. ►Table 4 provides an overview of the recommendations of the leading guidelines for VTE prevention in pregnancy in women with prior VTE.

- *Recommendation 7*: All women with a prior VTE should receive postpartum prophylaxis for at least 6 weeks. Women with prior VTE caused by a strong transient non-hormonal risk factor have a low risk of VTE recurrence during pregnancy if no further risk factors are present and therefore should receive only postpartum prophylaxis. Women with an unprovoked VTE, with a prior hormone or pregnancy-associated VTE or with persistent additional risk factors are considered to be at intermediate or high risk or recurrence and should therefore receive pharmacologic thromboprophylaxis throughout the pregnancy and the postpartum period.

Women with Prior VTE on Long-Term Anticoagulation Therapy

All women of childbearing age who require long-term anticoagulant therapy due to prior VTE should be instructed that pre-pregnancy counselling is mandatory if the woman wishes to become pregnant. First, all oral anticoagulants, i.e., vitamin K antagonists (VKAs) or direct oral

Table 4 International guideline recommendations for thromboprophylaxis in women with previous VTE

History	Presence and risk category for thrombophilia[a]	Risk period: antepartum (AP) vs.postpartum (PP)	ACCP, 2012[40]	SOCG, 2014[41]	RCOG, 2015[51]	ACOG[52]	ASH, 2018[50]	GTH, 2019
Prior VTE, provoked by a transient risk factor (unrelated to pregnancy or estrogen)	No	AP	–	–	+[b]	–	–	–
		PP	+	+	+	+/–[c]	+	+
	Yes: low risk	AP	–	+	+	Not addressed	–	+/–[d]
		PP	All guidelines recommend postpartal pharmacologic thromboprophylaxis					+
	Yes: high risk	AP	–	+	+	+	–	+
		PP	All guidelines recommend postpartal pharmacologic thromboprophylaxis					+
Prior VTE in the context of exogenous estrogen, pregnancy or unprovoked	No	AP	All guidelines recommend ante- and postpartal pharmacologic thromboprophylaxis irrespective of an underlying thrombophilia.					+
		PP						+
	Yes: low risk	AP						+
		PP						+
	Yes: high risk	AP						+
		PP						+

Abbreviations: ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians and Gynecologists; ASH, American Society of Hematology; GTH, The Working Group in Women's Health of the Society of Thrombosis and Haemostasis; RCOG, Royal College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, venous thromboembolism.

[a]Definitions of low- versus high-risk thrombophilias differ in the guidelines. Factor V Leiden (FVL) and prothrombin gene heterozygosity are considered low risk by all six organizations. Homozygosity or compound heterozygosity for FVL and prothrombin gene mutation are considered high risk by all six organizations. Protein C or S deficiency is considered high risk only by RCOG and GTH in the case of severe deficiency (PC activity $< 50\%$, PS deficiency $< 40\%$). Antithrombin deficiency is considered high risk by ACOG, RCOG, SCOG and GTH in case of severe deficiency (AT deficiency $< 60\%$).

[b]AP prophylaxis is recommended at 28 weeks in women in whom the prior VTE was provoked by major surgery in the case of no additional risk factors; in the case of additional risk factors prophylaxis is recommended throughout the antepartum period.

[c]PP prophylaxis is recommended if the patient has additional risk factors (first-degree relative with a history of a thrombotic episode, or other major thrombotic risk factors, e.g., obesity, prolonged immobility and caesarean delivery).

[d]May consider thromboprophylaxis based on the presence and number of other VTE risk factors.

anticoagulants (DOACs), cross the placental barrier and therefore have the potential to harm the foetus. Second, the risk of VTE recurrence increases with ongoing pregnancy. Third, the risk of bleeding complications under continued anticoagulant treatment must be considered. Thus, the woman must be informed about the risks of oral anticoagulant therapy before pregnancy occurs. LMWHs are the preferred anticoagulant agents in pregnancy. Based on the individual thrombotic risk, either therapeutic-dose weight-adjusted LMWH or an intermediate-dose regimen has been recommended as rational options.[40] In the German ETHIG trial, which included 810 pregnant women and analysed the management strategy for thromboprophylaxis according to the individual risk profile, no recurrent VTEs were observed in 66 pregnant women with acute VTE in pregnancy who were treated with 50 to 75% of the therapeutic dose from the third week onwards.[70]

Women on Anticoagulation Therapy with a DOAC

The oral direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban), collectively referred as DOACs, are currently widely used as therapeutic alternatives to VKA due to their efficacy, safety and convenience. Animal studies in rats and rabbits have shown that dabigatran, rivaroxaban and edoxaban cause reproductive toxicities. Animal studies with apixaban have shown no direct or indirect harmful effects.[71] However, in a human ex-vivo placenta model, Bapat et al demonstrated that apixaban crosses the term human placenta from the maternal to the foetal circulation, and estimated that foetal apixaban levels are 35 to 90% of the corresponding maternal levels.[72] The authors have previously published similar results for dabigatran and rivaroxaban.[73,74]

Only recently Lameijer et al reported a study of 236 DOAC-exposed pregnancies from the literature, for which pregnancy outcomes were available in 140 women (59%).[75] Thirty-nine pregnancies (17%) were electively terminated. In the remaining pregnancies, the live birth and miscarriage rates were 68 and 31%, respectively. Foetal and neonatal abnormalities were reported in eight pregnancies (7.4%). Thus far, no systematic clinical data are available for pregnancy outcomes after DOAC exposure. A multi-centre, international registry is currently underway to collect both retrospective and prospective data on women exposed to DOACs during pregnancy (International Society on Thrombosis and Haemostasis [ISTH], 2015). According to current evidence, an increased reproductive risk has to be considered, and therefore, DOACs must not be used during pregnancy. In 2016, the ISTH recommended that women

treated with DOAC who desire to become pregnant should be switched to an alternative anticoagulant (e.g., warfarin or LMWH) prior to pregnancy.[76] However, evidence is not available showing that switching from a DOAC to warfarin reduces foetal risks. Considering the data from more recent studies[77] and the short half-life of DOACs (i.e., 9–17 hours) compared with VKA, women on DOAC therapy can be offered two options:

- Replacement of DOAC with LMWH before conception is attempted.
- Maintenance of DOAC therapy during conception and immediate performance of a pregnancy test when a missing or delayed menstrual period occurs, with a substitution of LMWH for DOAC as soon as pregnancy is confirmed.

If pregnancy occurs accidentally while the woman is receiving DOAC therapy, termination of pregnancy is not recommended. However, it is suggested that patients should receive non-directive counselling. Early obstetric review and foetal monitoring is recommended to women with DOAC exposure when pregnancy is continued.

- *Recommendation 8*: Women of childbearing age who are treated with a DOAC must be informed about the potential teratogenic effects of these anticoagulants. If a woman on long-term DOAC therapy wishes to become pregnant, preconception counselling must be offered on how and when to switch to LMWH.
- *Recommendation 9*: If the woman has a regular monthly menstrual cycle and clearly understands the increased risk of miscarriage and embryopathy if the DOAC is continued after the sixth week of gestation (i.e., ≥14 days after the missed day of expected menses), we recommend the continuation of DOAC therapy and a switch to LMWH as soon as a pregnancy is confirmed. For women with an irregular menstrual cycle, we advocate a switch to LMWH before conception. However, both options should be discussed with the woman, and the woman's own preference should be considered.
- *Recommendation 10*: According to current evidence, the risk of foetal anomalies after DOAC exposure during early pregnancy appears to be low. Thus, we do not recommend an induced abortion after DOAC exposure but recommend first- and second-trimester screening for foetal anomalies.

Women on Anticoagulation Therapy with VKA

The period of organogenesis occurs at an embryonic age of 4 to 8 weeks, which corresponds to a gestational age of 6 to 12 weeks. This period carries the highest risk of malformation.[78] VKAs cross the placenta, and VKA exposure during the first trimester can result in foetal malformation. The precise incidence of coumarin embryopathy that predominantly comprises nasal and limb hypoplasia is unknown, as different retrospective and prospective observational studies report widely ranging incidence, but is most likely less than 10%.[79] Only two VKA embryopathies were observed in 280 pregnant women who were exposed to phenprocoumon, and no embryopathy was detected when anticoagulant therapy was terminated before the fifth gestational week.[80] A recently published German observational study compared 408 pregnancies with phenprocoumon exposure during the first trimester to 1,642 pregnancies that were not exposed to VKA. No typical coumarin embryopathy was observed in the phenprocoumon-exposed group. However, women who took phenprocoumon after the seventh gestational week presented a fivefold increased risk of birth defects (10.8%) compared with women who stopped taking phenprocoumon prior to the completion of 5 gestational weeks (2.4%).[81]

Furthermore, VKA can cause foetal bleeding at any stage of pregnancy and increase the risk of pregnancy loss.[80,82,83] VKA therapy for treatment and secondary prevention of VTE is generally avoided during pregnancy. Termination of VKA therapy before the sixth week of gestation will minimize the risk of foetal malformation, whereas exposure to warfarin after the 12th week of gestation is unlikely to cause coumarin embryopathy. Rarely, concomitant disease necessitates VKA therapy during pregnancy (e.g., prosthetic heart valves), in which case we refer to the corresponding guidelines.[84,85] The risk for foetal complications has been demonstrated to be dose-related and is considered low when the mean daily warfarin dose is less than 5 mg.[86] However, phenprocoumon is the predominantly used VKA in Germany, and it is important to note that warfarin and phenprocoumon substantially differ in their half-lives. The effective half-life of warfarin ranges between 36 and 42 hours, whereas that of phenprocoumon is 5 to 6 days.[87] Women taking phenprocoumon or warfarin prior to conception should be counselled about the foetal and maternal risks and should devise a clear plan concerning how and when to switch to LMWH. According to current international guidelines on warfarin and based on data from a German study showing a lack of coumarin-related embryopathies in pregnant women when phenprocoumon was terminated no later than the fifth gestational week, women on VKA therapy can be offered two major options[40,51]:

1. Replacement of VKA with LMWH before conception is attempted.
2. Maintenance of VKA therapy during conception with the immediate performance of a pregnancy test when a missing or delayed menstrual period occurs, and the substitution of LMWH for VKA as soon as a pregnancy is confirmed.

When choosing the first approach, the inconvenience of subcutaneously applied LMWH therapy in the longterm must be considered. For most couples trying to conceive, the odds that a woman will become pregnant are 15 to 25% in any particular month. In the general population, which covers all ages and includes individuals with fertility problems, 84% of women are estimated to conceive within 1year of unprotected sexual intercourse.[88] Furthermore, adverse side effects (e.g., osteopenia) and the higher costs of long-term heparin therapy must be considered.[89,90]

- *Recommendation 11*: Preconception counselling is mandatory if a woman on VKA therapy wishes to become pregnant. Women must be informed about foetal and

maternal risks of anticoagulant therapy. Pros and cons of the different treatment options, i.e., switching to LMWH before conception or immediately after the diagnosis of pregnancy but definitely before the sixth week of gestation, must be critically discussed with the women, and the patient's preference should be respected in decision making.

- *Recommendation 12*: According to current evidence, the risk of foetal anomalies after VKA exposure during early pregnancy appears to be low. Thus, an induced abortion after VKA exposure before the sixth week of gestation is not justified. Instead, first- and second-trimester screening for foetal anomalies is recommended.

Parenteral Antithrombotic Agents

Because of their molecular weight and strong negative charge, heparins do not cross the placental barrier and do not pass into breast milk in significant amounts.[40] They are therefore the pharmacologic agents of choice for the prophylaxis and treatment of VTE during pregnancy and the postpartum period.[16,40,41,51,91] There is no evidence of teratogenicity or an increase in foetal bleeding risk with the use of LMWH or UFH. The small amounts of LMWH that have been found to be excreted into breast milk are not expected to have a clinically relevant effect on the nursing child because the bioavailability of oral heparin is very low.[40] Because oral anticoagulants cross the placenta barrier, routine use of VKA to prevent or treat VTE during pregnancy is not supported, and DOACs are contraindicated in pregnancy and breast-feeding women. Fondaparinux and danaparoid are therapeutic options if heparins are contraindicated due to adverse side effects.

Low-Molecular-Weight Heparins

In general, subcutaneously administered LMWH is preferred over UFH. In a 2005 systemic review, Greer and Nelson-Piercy investigated the outcomes of 2,603 women who were treated with prophylactic doses for thromboprophylaxis or adverse pregnancy outcomes and 174 women with acute VTE who were treated with therapeutic doses.[57] When a low-dose LMWH was used for thromboprophylaxis, VTE occurred in 0.84% of pregnancies. Significant bleeding, mainly from obstetric causes, occurred in 2% of cases: 0.42% antepartum major bleedings, 0.92% postpartum haemorrhage and 0.65% wound haematomas. There were no maternal deaths. More recent observational trials confirmed the low rate of thromboembolic and bleeding events in pregnant women treated with LMWH.[70,92–94] In comparison to UFH, LMWHs were associated with a substantially lower risk of adverse side effects, such as HIT, heparin-induced skin reactions, haemorrhage and osteoporosis.[57,58,95–97] Bleeding risk has also been reported to be lower for LMWH when compared with UFH.[98]

Administration of LMWH during Pregnancy

When prescribing LMWH, it is important to avoid multi-dose preparations. Multi-dose vials of LMWH contain benzyl alcohol and/or other preservatives and are therefore contraindicated in pregnancy. Prefilled, single-dose syringes are generally preservative-free and are recommended for use in pregnant women. At baseline, routine laboratory parameters, including blood cell count, serum creatinine level, transaminases, prothrombin time and activated partial thromboplastin time (aPTT), should be obtained in all patients. It is reasonable to also check the blood cell count and serum creatinine periodically during the course of pregnancy (e.g., at 6–8-week intervals). Due to the very low risk of HIT in pregnant women treated with LMWH, monitoring of platelet count is not advocated.[99]

LMWH can be administered during pregnancy at *different doses* (i.e., prophylactic, intermediate or therapeutic), and there is currently no evidence from adequate randomized controlled trials regarding the optimal dose regimen.[40] However, a randomized controlled open-label trial comparing prophylactic and intermediate doses of LMWH in pregnant women with a history of VTE is currently underway (Highlow-Study; ClinicalTrials.gov NCT01828697). Generally, women with risk factors for VTE but no prior VTE should receive LMWH at *prophylactic* doses. An *intermediate-dose regimen* can be considered for women considered to be at higher risk, but current internal guideline recommendations are not concordant.[40,41,52] We recommend LMWH at an intermediate dose (i.e., 50–75% of the therapeutic dose) for women with a personal history of VTE and high-risk thrombophilia (e.g., AT deficiency, homozygosity for FVL and PGM and combined thrombophilias) who do not receive long-term anticoagulation therapy. In addition, an intermediate dose can be recommended for women on long-term anticoagulation therapy before pregnancy, when the bleeding risk seems to be high. Women on long-term anticoagulation therapy who are supposed to be at high risk for recurrent VTE should be treated with *therapeutic doses* of LMWH during pregnancy (e.g., unprovoked PE or proximal DVT and high-risk thrombophilia). Due to a lack of evidence, the decision concerning the adequate dose regimen must be made on an individual basis with thorough consideration of the woman's risk of VTE and of bleeding. ►**Table 5** summarizes the dose regimens of LMWH and alternative antithrombotic agents.

The utility of measuring anti-factor-Xa levels for consecutive dose adjustments remains controversial in pregnant women receiving LMWH. No clinical endpoint studies have demonstrated an increase in efficacy and safety outcomes during the performance of anti-Xa monitoring and consecutive dose adjustment. Furthermore, the appropriate target range for LMWH treatment during pregnancy has not yet been defined. Thus, current guidelines do not recommend routine anti-Xa monitoring for prophylactic or therapeutic anticoagulation during pregnancy.[40,41,51,91] However, measurement of anti-Xa peak levels for therapeutic treatment may be considered in women at the extremes of body weight (i.e., <50 or >100 kg), or in women with other complicating factors such as severe renal impairment or severe thrombophilia.[100] If monitoring is performed, peak anti-Xa activity levels are measured 2 to 4 hours after the last injection in the steady state. The target of anti-Xa activity for standard prophylaxis in non-pregnant patients is between 0.1 and

Table 5 Dose regimens (daily dose) for pharmacologic thromboprophylaxis

Antithrombotic agent	Prophylactic dose	Intermediate dose	Therapeutic dose (weight-adjusted)
Low-molecular-weight heparin			
Dalteparin	1 × 5.000 IE	1 × 100–150 IE/kg 2 × 50–75 IE/kg	1 × 200 IE/kg 2 × 100 IE/kg
Enoxaparin	1 × 4.000 IE	1 × 100 IE/kg or 2 × 50 IE/kg	2 × 100 IE/kg 1 × 150 IE/kg
Nadroparin	1 × 2.850 IE	–	2 × 85 IE/kg or 1 × 171 IE/kg
Tinzaparin	1 × 4.500 IE	–	1 × 175 IE/kg
Alternative anticoagulants			
Fondaparinux	1 × 2.5 mg	–	1 × 7.5 mg ≤50 kg: 1 × 5 mg ≥100 kg: 1 × 10 mg
Danaparoid	2 × 750 IE	–	3 × 750–1,250 IE
Unfractionated heparin			
UFH	2–3 × 5.000 IE or 2 × 7.500 IE	–	80 IE bolus i.v., followed by 18 IE/kg/h i.v. or 2 × 150–250 IE/d s.c. target aPTT: 1.5 to 2 × baseline

Abbreviations: aPTT, activated partial thromboplastin time;IE, internationale Einheit (international unit); i.v., intravenous; s.c., subcutaneous; UFH, unfractionated heparin.

0.4 U/mL. For therapeutic anticoagulation, the dose of LMWH is titrated to maintain a target peak anti-Xa activity of approximately 0.6 to 1.0 units/mL when twice daily and 0.8 to 1.3 U/mLwhen LMWH once daily administration is used.[52] Because heparins exert their activity by binding to AT, their anticoagulant effect may be attenuated in AT-deficient women. Generally, therapeutic anti-Xa levels can be achieved by increasing heparin doses, which may require supra-therapeutic doses or the co-administration of AT.

- *Recommendation 13*: Women who require VTE prophylaxis in pregnancy or the puerperium and who are not on prior anticoagulant therapy should generally be treated with prophylactic-dose LMWH. If the risk of VTE is considered to be substantially increased (e.g., prior VTE and high-risk thrombophilia), an intermediate dose of LMWH should be considered. Women on anticoagulation therapy prior to pregnancy are generally treated with intermediate or therapeutic-dose LMWH during pregnancy. There is a lack of evidence from clinical trials concerning the optimal dose regimen. However, we recommend continuation of therapeutic-dose anticoagulation for those women who are on long-term anticoagulation therapy or who are treated for acute DVT and considered to be at high risk for VTE recurrence.

Unfractionated Heparin

UFH may be considered as an alternative to LMWH in women at high risk for bleeding complications, with severe renal impairment or peripartum when regional anaesthesia is considered. Fixed doses of UFH are administered subcutaneously two or three times daily (i.e., 2–3 × 5,000 IE/d or 2 × 7,500 IE/d) for prophylactic purposes. Treatment with therapeutic doses usually requires a continuous infusion and aPTT monitoring to achieve a 1.5- to 2.5-fold prolongation of the aPTT or an anti-Xa level of 0.3 to 0.7 U/mL.[40,100] It is important to note that the aPTT response to UFH during pregnancy is often attenuated, which has been attributed to elevated levels of heparin-binding proteins (acute phase reactants) and elevated factor VIII levels.[101] In these situations, the anti-Xa activity test is usually preferred for monitoring UFH with a target anti-Xa level of 0.35 to 0.7 U/mL.[102]

Complications and Contraindications to LMWH and UFH

Increased Risk of Bleeding

As outlined above, the benefits and risks of pharmacologic thromboprophylaxis should be assessed in every woman on an individual basis. Anticoagulant treatment is contraindicated in women with uncontrolled hypertension (i.e., systolic blood pressure > 200 mmHg, diastolic blood pressure > 120 mm Hg), acute ischaemic or haemorrhagic stroke within the previous 4 weeks and in women with a high risk of major bleeding.[51] The risk of bleeding is substantially increased in women with placenta praevia, known bleeding disorders (e.g., von Willebrand disease, thrombocytopenia or hereditary or acquired coagulopathy), severe renal disease (i.e., glomerular filtration rate≤ 30 mL/min) or severe liver disease (i.e., prolonged prothrombin time, presence of oesophageal or gastric varices).

Clinically Relevant Bleeding

If bleeding complications develop under treatment with LMWH during delivery or in the postpartum period, heparin should be stopped, and a haemostaseologist should be

consulted. Anti-embolism stockings (AES) and intermittent pneumatic compression (IPC) devices can be used to reduce the risk of VTE in situations where anticoagulation therapy is contraindicated.[40,41,91,100] Thromboprophylaxis can be restarted as soon as the bleeding risk decreases. A reduction of heparin doses and administration of UFH instead of LMWH should be considered following severe bleeding. UFH may be preferred over LMH due to its shorter half-life and because its anticoagulant activity can completely be reversed by protamine sulfate. If bleeding occurs, the risks and benefits of antithrombotic treatment in these women should be reassessed.

Heparin-Induced Thrombocytopenia

HIT is a severe, immunologically mediated adverse drug reaction to UFH or less common to LMWH. Antibodies directed against complexes of heparin and platelet factor-4 cause platelet activation that can result in arterial and venous thrombosis.[103] LMWH and UFH are contraindicated in all patients with acute or prior HIT. However, the risk of HIT during pregnancy is thought to be very low (approximately1 in 4,000 pregnancies with exposure to heparin).[104] In a meta-analysis of 2,777 pregnancies during which LMWH was administered, no case of HIT was reported.[57] Therefore, current guidelines do not advocate routine monitoring of the platelet count in women treated with LMWH.[40,41,57,104,105] However, in pregnant post-operative women (e.g., after caesarean section) or those who receive UFH for more than 5 days, platelet count monitoring every 2 to 3 days between days 4 and 14 is mandatory. Because HIT is a life-threatening condition, clinical suspicion (i.e., an intermediate or high 4-T score) requires immediate discontinuation of heparin therapy and switching to a therapeutic dose of a non-heparin alternative anticoagulant.[103,104] However, as thrombocytopenia is not uncommon during pregnancy, other pregnancy-specific causes must be differentiated (e.g., gestational thrombocytopenia, preeclampsia, HELLP [haemolysis, elevated liver enzymes, low platelet count] syndrome).[106,107]

Heparin-Induced Allergic Skin Reactions

Heparin-induced skin reactions are primarily caused by delayed-type hypersensitivity (the so-called type IV allergic reaction) and usually present with itching erythema or red plaques at sites of heparin injection.[108] Allergic skin reactions have been observed in up to 20% of women treated with heparins throughout pregnancy.[109] The most pragmatic therapeutic option is to switch to another heparin. However, the cross-reactivity is high (33–73%), and it has been shown that high-molecular-weight heparins are more likely to induce skin reactions.[110] In cases of several cross-reactions, treatment with an alternative anticoagulant, such as fondaparinux or danaparoid, may be considered.

Heparin-Induced Osteoporosis

The long-term use of heparins during pregnancy may increase the rate of bone resorption.[111,112] Heparin-associated osteoporotic fractures due to osteopenia have been observed in 2 to 5% of patients treated with UFH in the long term, and a significant reduction of bone mass has been reported in up to 33% of cases.[40] The fracture risk is assumed to be substantially lower for LMWH, which has been attributed to the lower affinity of LMWH to osteoblasts and osteoclasts. Whether the use of prophylactic calcium supplementation in expecting mothers avoids heparin-induced osteopenia and reduces the risk of bone fractures has not been investigated.

- *Recommendation 14*: HIT in heparin-treated pregnant women is extremely rare. If HIT is suspected during pregnancy, consultation of a haemostaseologist or experienced thrombosis specialist is recommended to determine whether alternative anticoagulants, such as danaparoid or fondaparinux, are needed.

Alternative Anticoagulant Agents

There is less information on the foetal effects of the use of heparin-like anticoagulants, such as fondaparinux and danaparoid, and experience with their administration during pregnancy is limited.[113–115] Therefore, these substances are not recommended for routine use in pregnancy. Instead, their use should be limited to patients with definite contraindications to heparins, such as HIT or severe allergic reactions, as mentioned earlier.[16,40,41,51] In this context, the longer half-life of fondaparinux (i.e., 15–20 hours) and danaparoid (i.e., 22–24 hours) is a disadvantage, especially during the peripartum period.

Fondaparinux is a synthetic pentasaccharide factor-Xa inhibitor that, like LMWH, exerts its actions via high-affinity reversible binding to AT. However, there is evidence of minor placental passage of fondaparinux.[116,117] Dempfle reported that drug levels were one-tenth of maternal levels in umbilical cord blood in anti-Xa and aPTT assays.[117] Fondaparinux has also been found in the milk of lactating rats, and although it is unlikely that a negatively charged oligosaccharide will pass the intestinal barrier or appear in significant amounts in the neonatal blood, its use is not advocated in breast-feeding women.[40] Recently, de Carolis et al identified 65 cases treated with fondaparinux during pregnancy and reported pregnancy outcomes.[118] Overall, obstetric complications occurred in 27.5% of patients; there were 13 cases (20%) with spontaneous miscarriage, one ectopic pregnancy (1.5%) and two cases of intrauterine foetal growth retardation (3%). Thirty-nine women started fondaparinux therapy in the first trimester of pregnancy. Of the 13 miscarriages, 12 occurred in women with a history of previous pregnancy loss. Only one pregnancy was electively terminated due to foetal anomalies (Fallot's tetralogy and Dandy–Walker syndrome).[119] The vast majority of women were treated with fondaparinux due to hypersensitivity to different LMWHs. Thus, although experience is limited, it seems that fondaparinux is a reasonable option if there is a need for anticoagulant thromboprophylaxis or treatment in pregnancy and heparins cannot be used. However, there are only sporadic case reports in which fondaparinux was used to treat HIT during pregnancy.[120–122] At present, experience with fondaparinux during pregnancy remains too limited to recommend its use over danaparoid in cases of suspected HIT.

Danaparoid is a heparinoid that, like fondaparinux and LMWH, exerts its action by inhibiting activated factor X. In pregnant women with current HIT or HIT, an alternative anticoagulation therapy with danaparoid is recommended because it is an effective antithrombotic agent that does not cross the placental barrier and has low cross-reactivity with UFH and LMWH.[40] No anti-Xa activity was detected in samples of foetal cord blood, and none or very low (i.e., <0.07 U/mL) levels were found in samples of maternal breast milk.[115] However, the quality of evidence regarding the efficacy and safety of danaparoid during pregnancy is limited. Magnani reviewed 91 pregnancies in 83 women treated with danaparoid between 1981 and 2009.[115] Women were treated for a medium duration of 14 weeks during pregnancy with danaparoid, either because of HIT ($n = 47$) or due to allergic skin reactions ($n = 44$). No foetal outcome was available for eight cases. The remaining 83 pregnancies, including two twin pregnancies, resulted in 75 live births (90.4%), seven early spontaneous miscarriages (8.4%), one neonatal death after caesarean section at 28 weeks of gestation because of foetal growth retardation and one termination during major maternal surgery (1.2%). There were two maternal deaths (2.2%) due to fatal placental bleeding complications (placenta praevia, abruptio placentae) and four non-fatal bleeding complications (4.4%). Six thromboembolic events (6.6%) occurred during treatment with danaparoid, with all except one patient with acute HIT and recent VTE. In summary, danaparoid seems to be a reasonable option in pregnancy and the postpartum period when there is a requirement for anticoagulant prophylaxis and treatment and heparins cannot be used.

Mechanical Thromboprophylaxis

There are no trials supporting the use of AES, graduated compression stocking (GCS) or IPC during pregnancy and the postpartum period. Recommendations are therefore extrapolated from studies of non-pregnant patients. In general, pharmacological thromboprophylaxis should be preferred over mechanical prophylaxis because it is more effective in reducing the risk of VTE (RR: 0.58; 95% CI: 0.35–0.96).[91] Mechanical prophylaxis may be considered as an adjunct to pharmacologic prophylaxis, but it seems to be dispensable for the majority of patients. However, the use of AES and IPC is recommended in women who are hospitalized during pregnancy or postpartum and in whom the use of anticoagulants is contraindicated, e.g., because of active bleeding or a high risk of bleeding. Current guidelines recommend GCS for the treatment of leg swelling in cases of acute DVT or symptomatic post-thrombotic syndrome. They may also be effective to reduce the risk of VTE, but due to a lack of evidence, they cannot be recommended for routine use in primary thromboprophylaxis.

- *Recommendation 15*: The use of compression stockings is recommended for pregnant women with symptomatic chronic venous insufficiency due to post-thrombotic syndrome or varicosis. IPC should be considered for patients in whom the use of anticoagulants is contraindicated but who have a clear indication for antithrombotic therapy.

Thromboprophylaxis during Labour and Delivery

Vaginal delivery remains the preferred mode of delivery in women who receive antithrombotic treatment for the prevention or therapy of pregnancy-associated VTE. Because caesarean section is associated with higher blood loss and a greater risk of VTE compared with vaginal delivery, caesarean delivery should be reserved mainly for patients with obstetric indications.[123]

- *Recommendation 16*: We recommend that pregnant women who receive antithrombotic therapy during pregnancy be counselled in a timely manner (e.g., from the 32nd to 36th weeks of gestation) about issues of delivery and options for neuraxial anaesthesia and alternative pain reduction during delivery.

Vaginal Delivery

Upon the onset of labour or starting induction of labour or at least 12 hours before a caesarean section, the administration of prophylactic-dose LMWH should be discontinued.[40,41,51] For women on an intermediate or therapeuticdose, LMWH should be discontinued at least 24 hours before delivery. The risk of bleeding may be increased when delivery takes place within shorter periods after the last injection. However, at prophylactic doses, the overall bleeding risk remains low. If labour is prolonged and the risk of thrombosis is thought to be high, the administration of additional heparin doses has been suggested in consideration of the anticipated time of delivery and maternal bleeding risk.[51] Because of its shorter half-life, UFH has been preferred over LMWH in such cases. In the absence of bleeding complications, LMWH therapy at prophylactic doses can be resumed after a minimum of 4 to 6 hours.[91] Intermediate or therapeutic-dose LMWH should be restarted no sooner than 6 to 12 hours after vaginal delivery.[16]

Delivery by Caesarean Section

Thromboprophylaxis is generally not recommended after elective caesarean section in low-risk patients, but it is recommended to women with additional risk factors, e.g., postpartum infection or major postpartum haemorrhage.[47,91] Prophylactic-dose LMWH can be initiated or resumed 6 to 12 hours after caesarean delivery. If intermediate- or therapeutic-dose LMWH is required, therapy should be restarted no sooner than 12 to 24 hours after caesarean section, provided that there were no bleeding complications.[16] The decision for or against pharmacologic thromboprophylaxis after caesarean section as well as the duration of antithrombotic therapy depend on the clinical situation. Pharmacologic thromboprophylaxis after elective caesarean section in the absence of additional risk factors is not generally recommended.[34,42,43] In cases of additional transient (e.g., wound infection or surgery in the puerperium) or several persistent risk factors (e.g., low-risk thrombophilia and BMI $\geq 30\,kg/m^2$), pharmacologic thromboprophylaxis for at least 7 to 10 days up to 6 weeks postpartum should be considered. It has been suggested that after caesarean section performed as an emergency, women should receive thromboprophylaxis with LMWH for at least

7 days.[40,47,51] Women considered to be at high risk for VTE (e.g., women treated with LMWH antenatally due to prior VTE or thrombophilia or who suffer from known high-risk thrombophilia in whom thromboprophylaxis was not initiated during pregnancy) should be treated with LMWH for approximately 6 weeks postpartum.

Use of Neuraxial Anaesthesia

The incidence of bleeding complications (e.g., spinal epidural haematoma) after neuraxial anaesthesia is unknown. The risk of bleeding in women at the time of delivery is considered to be as low as 1:100,000 to 1:186,000.[91] The risk increases with the use of heparins, low-dose aspirin, thrombocytopenia or unknown bleeding disorders. According to the current version of the European Society of Anaesthesiology (ESA) on neuraxial anaesthesia in patients receiving antithrombotic agents, the use of LMWH at *prophylactic* doses must be discontinued for at least 12 hours before catheter insertion, and treatment can be resumed a minimum of 4 hours after catheter removal provided that haemostasis is confirmed and there are no neurological symptoms. Because of the shorter half-life of UFH, switching from LMWH to UFH at term (i.e., after the 37th week) allows neuraxial anaesthesia after a minimum of 4 to 6 hours following the last UFH injection.[124] An overview of the recommended time intervals before catheter insertion or removal in anticoagulated patients is presented in ►Table 6.[124,125] The implications of treatment with LMWH for regional anaesthesia and alternative options for intrapartum analgesia should be discussed with the woman prior to labour or caesarean section.

Neuraxial anaesthesia is contraindicated in pregnant women who receive LMWH at *intermediate* or *therapeutic doses* because LMWH must be discontinued at least 24 hours before catheter insertion.[124] Spontaneous labour usually does not meet this time interval. Therefore, the majority of women with therapeutic anticoagulation can be expected to deliver without neuraxial anaesthesia. The induction of labour or switching to UFH at term may be considered. In women receiving UFH, heparin must be discontinued for at least 4 to 6 hours if it is administered intravenously and for at least 8 to 12 hours if it is administered subcutaneously.[124] If the level of anticoagulation therapy is uncertain, aPTT testing or, in cases of LMWH, an assessment of anti-Xa levels can be helpful. A recent platelet count should also be available before invasive procedures are performed. Women on intermediate or therapeutic anticoagulation who have received neuraxial anaesthesia should be monitored closely for the development of a spinal haematoma.

- *Recommendation 17*: Upon the onset of labour or starting induction or at least 12 hours before a caesarean section, the administration of LMWHs should be discontinued. Neuraxial anaesthesia can be performed after a minimum of 24 hours after a therapeutic dose, 12 hours after a prophylactic dose of LMWH or at least 4 to 6 hours after an intravenous infusion of UFH has been administered, when the aPTT is normal. Women on therapeutic anticoagulation who have received neuraxial anaesthesia should be monitored closely for the development of a spinal haematoma.

Antithrombotic Therapy in the Postpartum Period

Heparin, warfarin and acenocoumarol treatments during the lactation period are considered safe for the newborn.[40] If thromboprophylaxis with prophylactic-dose LMWH is established or continued for 6 weeks postpartum, it may be practical to maintain treatment with LMWH therapy because the woman is used to injection and multiple international normalised ratio (INR) testing, while titrating warfarin can be avoided. If intermediate or therapeutic doses or longer periods of antithrombotic therapy are required, switching to warfarin with a target INR between 2.0 and 3.0 should be considered.

Table 6 Neuraxial anaesthesia in anti-coagulated patients: minimum time intervals without anticoagulation before and after catheter placement and removal[124,125]

Antithrombotic medication	Half-life (h)	Before puncture/before catheter removal (h)	After puncture/after catheter removal (h)
Prophylactic dose regimen			
UFH, 2–3 × 5.000 or 2 × 7.500 IE/d	1.5–2	4	1
LMWH, prophylactic dose	4–6	12	4
Fondaparinux, 1 × 2.5 mg/d	15–20	36–42	6–12
Danaparoid, 2 × 750 IE/d	22–24	48	3–4
Therapeutic dose regimen			
LMWH, therapeutic dose	4–6	24	4
UFH, therapeutic dose	2–3	i.v. → 4–6 s.c. → 8–12	1
Fondaparinux, therapeutic dose	15–20	Neuraxial anaesthesia should be avoided due to a long half-life and potential accumulation	
Danaparoid, therapeutic dose	24		

Abbreviations: IE, internationale Einheit (international unit); i.v., intravenous; s.c., subcutaneous;LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Warfarin and acenocoumarol are highly protein-bound and are not expected to appear in significant amounts in breast milk.[40,126,127] Concerns have been raised regarding the use of the less polar, more lipophilic phenprocoumon. Despite the limited data in the published literature, phenprocoumon levels in human breast milk are presumed to be too low to affect the coagulation parameters of the newborn.[128]

If a VKA is considered as an alternative to LMWH treatment during breast-feeding, conversion from LMWH to VKA should be delayed for at least 5 to 7 days after delivery to minimize the risk of haemorrhage during the period of overlap of LMWH and VKA treatment.[51] Vitamin K prophylaxis should be consistently administered to the newborn in the first few postnatal weeks and comprises the parenteral application of vitamin K in the immediate postpartum period and oral supplementation as part of the regular preventative medical examination.[128]

To date, there are no clinical data on the effect of maternal DOAC therapy on the breast-fed child. Therefore, the manufacturers of these agents recommend against using these medications in breast-feeding women.[71]

- *Recommendation 18*: Anticoagulant therapy in the postpartum period can be continued using LWMH or switched to VKA with an overlapping phase and frequent INR monitoring. A sufficient amount of a vitamin K supplement must be provided to the newborns of breastfeeding women during VKA treatment.

Conclusions

Because there is a lack of adequate study data, management strategies for the prevention of VTE during pregnancy has mainly been deduced from case–control and observational studies and extrapolated from recommendations for non-pregnant patients. The decision for or against pharmacologic thromboprophylaxis must be made on an individual basis weighing the risk of VTE against the risk of adverse side effects such as severe bleeding complications. A comprehensive, multidisciplinary approach is often essential as the clinical scenario is made more complex by the specific obstetric context, especially in the peripartum period. We conclude that there is an urgent need for well-designed prospective studies to compare different management strategies in women with pregnancy-associated VTE.

Conflict of Interest

The authors declare that they have no conflict of interest.

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