Review

Treatment of pregnancy-associated venous thromboembolism – position paper from the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH)

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Summary: Venous thromboembolism (VTE) is a major cause of maternal morbidity during pregnancy and the postpartum period. However, because there is a lack of adequate study data, management strategies for pregnancy-associated VTE must be deduced from observational studies and extrapolated from recommendations for non-pregnant patients. In this review, the members of the *Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH)* have summarised the evidence that is currently available in the literature to provide a practical approach for treating pregnancy-associated VTE. Because heparins do not cross the placenta, weight-adjusted therapeutic-dose low molecular weight heparin (LMWH) is the anticoagulant treatment of choice in cases of acute VTE during pregnancy. No differences between once and twice daily LMWH dosing regimens have been reported, but twice daily dosing seems to be advisable, at least peripartally. It remains unclear whether determining dose adjustments according to factor Xa activities during pregnancy provides any benefit. Management of delivery deserves attention and mainly depends on the time interval between the diagnosis of VTE and the expected delivery date. In particular, if VTE manifests at term, delivery should be attended by an experienced multidisciplinary team. In lactating women, an overlapping switch from LMWH to warfarin is possible. Anticoagulation should be continued for at least 6 weeks postpartum or for a minimum period of 3 months. Although recommendations are provided for the treatment of pregnancy-associated VTE, there is an urgent need for well-designed prospective studies that compare different management strategies and define the optimal duration and intensity of anticoagulant treatment.

Key words: Venous thromboembolism, deep vein thrombosis, pulmonary embolism, low molecular weight heparin, pregnancy, postpartum

Introduction

There is a paucity of studies addressing the diagnostic strategies and the risks and benefits of antithrombotic therapy during pregnancy. In a recently published article, we systematically reviewed the current evidence for the diagnostic management of deep vein thrombosis (DVT) and pulmonary embolism (PE) and provided a diagnostic algorithm for their diagnosis during pregnancy and the postpartum period. The present article is a state of the art review of treatment strategies for pregnancy-associated venous thromboembolism (VTE). It is clear that pregnant women have been excluded from all major phase III trials that have investigated the efficacy and safety of different anticoagulant regimens. Because of a lack of appropriate study data, treatment strategies are mainly extrapolated from studies of non-pregnant patients while considering the specific risks and benefits in both pregnant women and foetuses. Pregnant women who present with acute VTE, particularly in cases of proximal DVT or PE, should be hospitalised or followed closely when treated as outpatients. The risk of VTE recurrence is the highest within the first 2–3 weeks after the initial diagnosis.

Laboratory tests and biomarkers

Before or during the initiation of anticoagulant therapy, routine blood parameters, such as complete blood cell counts, prothrombin times, activated partial thromboplastin times (aPTTs), renal and liver function tests and electrolyte testing should be performed to exclude severe coagulation disorders and rule out renal or hepatic dysfunction. Although no specific data are available for pregnant women, testing for brain natriuretic peptide (BNP) or N-terminal (NT-) proBNP and for the cardiac troponins I or T in women with confirmed PE may identify cases with compromised right ventricular function or myocardial injury and a consequently increased risk of early death [1]. These women require special care and close monitoring, and should initially be transferred to an intensive or intermediate care setting.

Anticoagulant therapy during pregnancy

Low-molecular-weight heparins (LMWH) are considered the anticoagulants of choice in pregnancy-associated VTE because LMWH do not cross the placenta and do not appear at significant levels in breast milk. Although a Cochrane Review stated that there was no evidence from randomised controlled trials regarding the efficacy of anticoagulant therapy for DVT in pregnancy [2], two systemic reviews of LMWH use in pregnant women have confirmed their efficacy and safety, which were consistent with those in non-pregnant women [3, 4]. Compared to unfractionated heparin (UFH), LMWH were associated with a substantially lower risk of adverse side effects, such as heparin-induced thrombocytopenia (HIT), haemorrhage, and osteoporosis [3–7].

However, UFH may be considered an alternative if LMWH cannot be used or if UFH seems to be advantageous over LMWH, e.g., in women at high risk of bleeding complications or in women with severe renal impairment. Women with confirmed PE and haemodynamic compromise who are candidates for subsequent thrombolysis should also receive UFH during the initial phase until definitive treatment decisions are reached [1]. Data obtained from non-pregnant patients have confirmed that LMWH are at least as effective as vitamin K antagonists (VKA) in preventing recurrent VTE and post-thrombotic syndrome (PTS) without increasing the risk of serious bleeding compared to VKA [8-10]. Although LWMH have not been officially approved for use in pregnancy, they have been widely used in pregnant women, and current guidelines therefore recommend LMWH as first-line anticoagulants during pregnancy [1, 8, 11–13].

Experience with the use of other heparin-like anticoagulants, such as fondaparinux and danaparoid, during pregnancy is limited [14–16]. They should be considered second-line drugs in cases in which severe side effects result from LMWH or UFH (e.g., heparin-induced skin lesions, HIT). VKA, such as phenprocoumon or warfarin, cross the placenta and have the potential to cause both teratogenicity and foetal bleeding. Women with pregnancy-associated VTE should therefore not be treated with VKA. There have not been any human studies assessing the safety and efficacy of novel oral anticoagulants (NOACs), such as the direct thrombin inhibitor dabigatran etexilate or the factor Xa inhibitors rivaroxaban, apixaban or edoxaban in pregnant or breast-feeding women, but these NOACs are thought to cross the placenta barrier, therefore leading to anticoagulation within the foetus, and can also be secreted into the breast milk. Animal studies of dabigatran and rivaroxaban revealed that they caused teratogenic effects, placental abnormalities, foetal haemorrhage and reduced foetal viability. Their use is therefore not recommended in pregnancy or during lactation [17–20].

Recommendation 1 – Heparins do not cross the placenta barrier. They are therefore the pharmacologic agents of choice for the treatment of VTE during pregnancy. In general, subcutaneously administered full-dose weight-adjusted LMWH is preferred over UFH. According to current evidence, there is no support for the routine use of VKA, NOACs, fondaparinux or danaparoid in uncomplicated pregnancy-associated VTE. However, fondaparinux and danaparoid are a therapeutic option if heparins are contraindicated due to adverse side effects.

LMWH – once or twice daily dosing

During the acute phase of DVT or PE, LMWH are usually administered in a full-dose, weight-adjusted, once-daily or twice-daily regimen. Table I describes the common dosing regimens used for the treatment of pregnancy-associated VTE. It has been suggested that a twice-daily regimen (e.g., dalteparin 100 IE/kg twice daily or enoxaparin 1 mg/kg twice daily) may be superior to once-daily dosing (e.g., tinzaparin 175 IE/kg once daily or dalteparin 200 IE/kg once daily) because of lower peak levels and the consequently lower bleeding risk [21, 22]. However, there are no clinical data to support this hypothesis. The glomerular filtration rate increases by approximately 50 % after the 15th week of gestation, and as a consequence, LWMH clearance is also expected to increase. However, the data on this topic are conflicting [21, 23]. Two studies investigating the pharmacological profile of enoxaparin in pregnancy revealed a decrease in peak aXa levels at 3 hours after subcutaneous injection and an increase in trough aXa activities, which the authors attributed to an increase in plasma volume and the apparent volume of distribution [24, 25]. The authors concluded that the consecutive prolongation of enoxaparin elimination half-life that was observed during the progress of pregnancy favoured a once-daily dose regimen in pregnant patients and that determining dose adjustments based on peak aXa levels may not be appropriate during pregnancy. No difference in clinical outcomes has been observed in

Table I. Low molecular weight heparins – once or twice daily dosing regimens

Twice daily dosing	Once daily dosing
Dalteparin 2 x 100 U/kg s.c.	Dalteparin 1 x 200 U/kg s.c.
Enoxaparin 2 x 1 mg/kg s.c.	Enoxaparin 1 x 1.5 mg/kg s.c. *
N.A.	Tinzaparin 1 x 175 U/kg s.c.
Nadroparin 2 x 85 U/kg s.c.	Nadroparin 1 x 171 U/kg s.c.

* A once daily dosing regimen is not licensed in some countries
Abbr.: N.A.: Not applicable.

small observational studies wherein women using once-daily and twice-daily regimens throughout pregnancy were compared [26, 27]. The recently updated Royal College of Obstetricians & Gynaecologists guidelines state that there is insufficient evidence to recommend whether LMWH should be given once daily or in two divided doses [13].

Recommendation 2 – Once or twice daily dosing regimens of full-dose weight-adjusted LMWH are acceptable for the treatment of acute VTE during pregnancy. On the basis of current evidence, once daily dosing seems to be suitable, and limits the number of injections. Although it is uncertain whether twice daily dosing is attended by a lower bleeding risk, the authors advocate switching to a twice daily dosing regimen perinatally because this may avoid high aXa levels at the time of delivery.

LMWH – maintenance therapy

Women with antenatal VTE are usually managed with LMWH for the remainder of pregnancy and during the postpartum period. There is no doubt regarding the use of a full-dose weight-adjusted LMWH regimen in the initial phase of VTE therapy. However, it remains unclear whether the initial therapeutic dose of LMWH can be reduced after several weeks to an intermediate dose [28]. A dose reduction to 50–75% of the initial dose has been successfully established in non-pregnant patients who were treated in the long-term with LMWH because there were contraindications to oral anticoagulants or because there were underlying malignancies [8, 29, 30]. Whether a comparable strategy is also safe in pregnant women is uncertain. Because the risk of VTE increases with the number of gestational weeks, and because higher LMWH doses may be required to maintain therapeutic aXa levels, a continued full-dose LMWH regimen may be reasonable unless maternal bleeding risk is substantially high. On the other hand, it can be argued that cancer patients are at a much higher risk of treatment failure than pregnant women, which strengthens the rationale for a dose reduction. Furthermore, reducing the intensity of anticoagulant therapy will very likely also reduce the risk of bleeding complications. The use of intermediate doses of LMWH may be an attractive alternative to the use of full-dose anticoagulants, particularly if limited venous thrombosis occurs during early pregnancy in association with transient risk-factors other than the pregnancy itself (e.g., distal DVT following immobilisation). No recurrent events were observed in a prospective study of 66 pregnant women suffering from acute VTE who were treated with 50–75% of the full therapeutic dose from the 3rd week onwards [31].

In a systemic review, Gandara et al. summarised the evidence from 4 studies that included 152 women with pregnancy-associated VTE who were treated with an intermediate LMWH dose for the secondary prevention of VTE throughout pregnancy [32]. An intermediate dose was defined as any dose lower than 75% of the full dose and higher than a prophylactic dose. When either LMWH or UFH were used during the acute full-dose treatment phase, no women experienced VTE recurrence. The authors identified only one recurrent DVT during ongoing pregnancy, and it occurred when a 50% dose reduction was performed within 7 days after the diagnosis of DVT. However, the studies included in this review were not intended to answer the question of optimal dosing of LMWH for the secondary prevention of VTE. Recently, the same authors published the results of an electronic survey that assessed current practices for the management of pregnancy-associated VTE in Canada [33]. Of the 69 physicians who completed the survey, more than 70% of the respondents favoured a long-term treatment with full doses of LMWH during pregnancy.

Recommendation 3 – Because there are no studies comparing full-dose LMWH to modified dose regimens in pregnant patients, it remains unclear whether the full therapeutic dose can be reduced to an intermediate dose regimen for the secondary prevention of VTE during ongoing pregnancy. In particular, a dose reduction should be considered during the course of pregnancy in women at high risk for bleeding complications or in whom the risk of VTE recurrence is supposed to be low.

Monitoring LMWH during pregnancy

It is still a matter of debate whether it is useful to use measurements of anti-factor-Xa (aXa) levels to determine consecutive dose adjustments in pregnant women receiving LMWH treatment. Inter-assay and inter-laboratory variability in aXa measurements have been described in non-pregnant and pregnant patients that were treated with therapeutic-doses of LMWH, and the validity of using peak aXa levels as a marker of antithrombotic activity has been questioned [23, 34–36]. Moreover, several prospective observational studies have demonstrated that only a few pregnant patients required dose adjustments according to aXa levels when enoxaparin, dalteparin or tinzaparin were administered at therapeutic doses [37–41] (Tab. II). In contrast, the results of other studies have indicated that higher LMWH doses are required to achieve therapeutic anti-Xa levels in progressing pregnancy. Jacobsen et al. treated 20 pregnant VTE patients with dalteparin (100 U/kg bid) and observed that a 10–20% higher dose of dalteparin was required to obtain therapeutic aXa levels than in non-pregnant women [42]. Barbour et al. measured

Table II. Monitoring anti-factor-Xa levels during pregnancy

Study	Patient number	Study design	Treatment regimen	Anti-factor-Xa target range	Dose adjustment, % in target range
Rodie, 2002 (37)	n = 33	Prospective observational	Enoxaparin 2 x 1 mg/kg	0.4 – 1.0 U/mL, 3 h after injection	Dose reduction in 3 cases (9.1 %)
Smith, 2004 (38)	n = 29	Multicentre prospective Observational	Tinzaparin 1 x175 U/kg	0.3 – 1.0 U/mL, 4 h after injection	Dose increase in 1 case (3.4 %)
Rey, 2000 (40)	n = 15	Observational	Dalteparin 2 x 100 U/kg	0.5 – 1.0 U/mL, 4 h after injection	No dose adjustment required
Friedrich, 2010 (39)	n = 15	Prospective observational	Enoxaparin 2 x 1 mg/kg	0.5 – 1.2 U/mL 3 – 4 h after injection (peak), 8 h after injection and trough	No dose adjustment required, all peak levels within the target range, 20% subtherapeutic after 8 hours, 73% subtherapeutic trough levels
Barbour, 2004 (43)	n = 13	Prospective observational	Dalteparin 2 x 100 U/kg	0.5 – 1.0 U/mL 2 – 4 h after injection (peak) and trough levels	Dose increase in 11 cases (85 %), dose reduction in 1 case (7.7 %), 85% subtherapeutic trough levels
Jacobsen, 2003 (42)	n = 20	Observational	Dalteparin 2 x 100-133 U/kg	0.5 – 1.0 U/mL 2 – 3 h after injection	Dose increase in 9/13 cases starting with 2 x 100 U/kg (69 %), no dose adjustment in 6/7 cases starting with 105 – 118 U/kg dose reduction in one case starting with 2 x 133 U/kg
Berresheim, 2014 (41)	n = 16	Retrospective	Enoxaparin 2 x 1 mg/kg	0.5 – 1.0 U/mL (VTE) 0.6 – 1.2 U/mL (MHV) 3.5 – 5 h after injection	No dose adjustment in 12 cases because of VTE, mean dose increased to 2 x 1.35 mg/kg in 4 anticoagulated cases because of MHV

Abbr.: VTE: Venous thromboembolism, MHV: Mechanical heart valve

peak and trough aXa levels in 13 pregnant women who received therapeutic doses of dalteparin (100 U/kg bid) and found that dose adjustment based on weight alone was inadequate to maintain aXa levels between 0.5 and 1.0 U/ml [43]. In their study, approximately 85 % of pregnant patients required a dose increase to achieve peak aXa activity in the therapeutic range, whereas the majority of trough levels were subtherapeutic (i.e., < 0.5 U/ml).

In the above-mentioned studies, a total of 141 pregnant women treated with different LMWHs were investigated. In these studies, there was no agreement regarding the optimal time interval that should be used between heparin injection and blood withdrawal to measure peak aXa levels. Some studies measured only peak aXa levels, whereas others also measured trough levels. Currently, no clinical endpoint studies have demonstrated an increase in efficacy and safety outcomes, such as VTE recurrence or bleeding risk, when aXa monitoring and consecutive dose adjustment are performed. Moreover, the existing data are insufficient to answer the question of how to monitor and adjust LMWH dosing to optimise anticoagulant treatment during pregnancy.

Thus, current guidelines do not generally recommend routine aXa monitoring during pregnancy [8, 11, 13]. The 2015 version of the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines states that measuring aXa peak levels 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 renal impairment, severe thrombophilia, and recurrent VTE despite anticoagulant therapy [13]. Because heparins exert their activity by binding to antithrombin, their anticoagulant effect may be attenuated in antithrombin-deficient women. Generally, therapeutic aXa levels can be achieved by increasing heparin doses, which may require supra-therapeutic doses or the co-administration of antithrombin [44].

However, a recent survey assessed current practices used to manage pregnancy-associated VTE, and revealed that 55/69 physicians performed aXa-monitoring in patients being treated with LMWH during pregnancy [33]. When LMWH monitoring and dose-adjustment are considered, measurements of aXa peak levels every 4-6 weeks should be taken using blood sampling within 2-4 hours after subcutaneous LMWH injection. No data have indicated a different aXa target range for pregnant women compared to non-pregnant patients. Therefore, dose adjustment may be performed to maintain a therapeutic aXa level (e.g., 0.6–1.0 U/mL when a twice daily regimen is used and 0.8–1.3 U/mL when LMWH is administered once daily) [45]. In clinical practice, women are advised to inject themselves in the morning to allow for blood sampling within 2–4 hours after subcutaneous LMWH injection.

Table III. Recommendations for UFH dose adjustment (modified after [45]). It may be advisable to adapt the aPTT target range to the local institution's aPTT reagent and clinical expertise

aPTT	aPTT ratio: aPTT/aPTT (baseline)	Bolus 80 U/kg followed by an infusion of 18 U/kg/h
aPTT < 35 s	1.00 – 1.19	Administer a bolus of 80 U/kg, then increase the infusion rate by 4 U/kg/h
aPTT 35 – 45 s	1.20 – 1.49	Administer a bolus 40 U/kg, then increase the infusion rate by 2 U/kg/h
aPTT 46 – 70 s	1.50 – 2.49	No change
aPTT 71 – 90 s	2.50 – 3.00	Decrease the infusion rate by 2 U/kg/h
aPTT > 90 s	> 3.00	Stop infusion for 1 h, then decrease the infusion rate by 3 U/kg/h

Abbr.: aPTT: Activated partial thromboplastin time

Recommendation 4 – According to current evidence, using routine aXa measurement to monitor LMWH therapy during pregnancy cannot be recommended. Clinical endpoint studies assessing the risks of VTE recurrence and bleeding complications are strongly needed to clarify whether pregnant women will actually benefit from monitoring and dose adjustment strategies. However, the measurement of aXa levels may be helpful when the risk of recurrent VTE is thought to be high, in cases of treatment failure (i.e., VTE recurrence despite adequate dosing), or when bleeding complications occur. In women at the extremes of body weight (i.e., < 50 or > 100 kg) and in those with renal insufficiency, aXa measurement may also be considered. We recommend the use of aXa monitoring and dose-adjustment to achieve therapeutic aXa levels in antithrombin-deficient women with pregnancy-associated VTE.

Anticoagulant therapy with UFH

Unfractionated heparin may be considered as an alternative when LMWH cannot be used or when UFH is thought to be advantageous over LMWH, for example, in women with acute VTE after the 36th week of gestation, in women suspected of having massive PE, in women at high risk of developing bleeding complications or in women with severe renal impairment. When UFH is given at therapeutic doses, the administration of a loading dose (e.g., 80 U/kg) is recommended and is usually followed by a continuous intravenous infusion (e.g., 18 U/kg/h) to achieve a 1.5- to 2.5-fold prolongation of the aPTT. Treatment with UFH at therapeutic doses requires monitoring of aPTT to achieve a therapeutic 1.5- to 2.5-fold prolongation of the aPTT and an aPTT level that corresponds to an aXa level of 0.3–0.7 U/mL [8, 11, 45]. In cases of intravenous administration, the aPTT must be determined 4-6 hours after the loading dose and subsequently after every change in infusion rate (Tab. III). When aPTT levels are within the therapeutic range, at least once daily testing must be performed.

UFH can also be administered subcutaneously through twice daily injections. In cases of subcutaneous administration, aPTT tests should be performed 5–6 h after injection to assure a therapeutic prolongation [45]. It is important to note that the aPTT response to UFH during pregnancy is often attenuated. This is probably because the levels of heparin-binding proteins, such as factor VIII and fibrinogen, increase during pregnancy. Consequently, higher heparin doses may be required to obtain aPTT values in the therapeutic range in pregnant women compared to those used in non-pregnant patients [13, 46, 47].

Platelet count monitoring

The risk of HIT during pregnancy is thought to be low (approximately 1 in 4000 pregnancies) [48]. Therefore, current guidelines do not advocate routine platelet count monitoring [13, 48, 49]. However, performing platelet count monitoring every 2–3 days between days 4 and 14 is recommended in pregnant women who are postoperative, who receive UFH for longer than 5 days [13, 49].

Anticoagulant therapy during delivery

The management of anticoagulated women who are at term is challenging, and in these cases, close collaboration between the obstetrician, the anaesthesiologist, the neonatologist and the haemostaseologist is required. In high-risk pregnancies, delivery should take place in a tertiary care centre with specialist multidisciplinary team care. Several delivery options are possible, including spontaneous labour and delivery, the induction of labour, and elective caesarean section. Because caesarean section is associated with higher blood loss, an increased risk of wound complications in anticoagulated women and a higher risk of VTE, it should be reserved mainly for patients with obstetric indications [21, 50–52]. Thus, vaginal delivery remains the preferred mode of delivery in women who are anticoagulated due to pregnancy-associated VTE.

Current guidelines recommend discontinuing LMWH at least 24 hours before caesarean section or the elective induction of labour [8, 13, 53]. However, many obstetricians do not consider the induction of labour to be necessary. As labour can begin at an unplanned time, it is important to advise anticoagulated women early that they must stop LMWH as soon as labour starts, which is indicated by either contractions or the rupture of membranes. A twice-daily administration of LWMH is recommended perinatally (e.g., 37th week of gestation) to avoid high peak levels and to lower the risk of postpartum bleeding complications. If labour is prolonged and the risk of VTE recurrence is thought to be high, the administration of additional pro-

Table IV. Neuraxial anaesthesia in patients treated with therapeutic doses of anticoagulants [58]. Minimum time intervals without anticoagulation before and after catheter placement and removal according to the recommendations of the European Society of Anaesthesiology: after 2 half-lives there will be 25% residual anticoagulant activity, which provides attenuated protection against thrombosis and a reduced bleeding risk, which generally allows the use of neuraxial anaesthesia. After 4–5 half-lives, anticoagulant rest-activities are expected to be as low as 3.1–6.2%. The half-life may be substantially prolonged in cases of severe renal impairment

Medication	Half-life	Before puncture/ before removal	After puncture/ after removal
UFH, therapeutic dose	2–3 h	i.v. → 4–6 h s.c. → 8–12 h	1 h
LMWH, therapeutic dose	4–6 h	24 h	2–4 h
Fondaparinux, therapeutic dose	15–20 h	Neuraxial anaesthesia should be avoided due to a long half-life and potential accumulation	
Danaparoid, therapeutic dose	24 h		

Abbr.: UFH: Unfractionated heparin, LMWH: Low molecular weight heparin

phylactic or intermediate heparin doses may be considered necessary in consideration of the anticipated time of delivery and the woman's risk of bleeding. The optimal time to restart the administration of anticoagulants postpartum is unknown. It may be reasonable to restart the anticoagulant therapy no sooner than 6–12 hours after vaginal delivery and 12–24 hours after caesarean section, depending on the amount of blood lost and the anticipated risk of recurrent VTE in the absence of anticoagulants. If the bleeding risk is thought to be high, the administration of anticoagulants can be restarted at a prophylactic dose (e.g., dalteparin, 5000 units; enoxaparin, 40 mg or tinzaparin, 3500 IU) and thereafter upgraded to intermediate or therapeutic doses of LMWH when adequate haemostasis has been obtained. The LMWH dose should be adjusted to the postpartum weight of the patient, because supratherapeutic levels of LMWH have been observed when the antenatal dose was continued postpartum [54].

In women in whom an acute proximal DVT or PE occurs after the 37th week of gestation, the risk of symptomatic PE during labour is substantially increased. In these cases, a planned delivery may be beneficial, either through the induction of labour or by elective caesarean section, because this allows events to be timed and minimises the duration of time spent without adequate anticoagulation and the risks of unscheduled delivery on full anticoagulation [8, 11, 13]. Women treated with LMWH may be switched to a continuous infusion of UFH at least 36 h before the induction of labour or caesarean section [11]. UFH has a shorter half-life and should be discontinued 4–6 hours before planned delivery. Alternatively, if the risk of PE is estimated to be markedly increased, the infusion rate may be down-regulated (e.g., 400–600 IE/h) [31] to maintain anticoagulation as long as possible, and the infusion may be discontinued for only the ejection phase of delivery. Infusion may then be restarted 4–6 h after delivery if there are no bleeding complications. A retrievable inferior vena cava filter may also be inserted and then removed postpartum to prevent PE during delivery. However, experience with these devices is very limited, and in consideration of the potential complications, it may be best to restrict IVC filter insertion to women in whom anticoagulation is contraindicated or in women with proven DVT who have recurrent PE despite adequate anticoagulation [8, 9, 55, 56]. Outside pregnancy, the use of IVC filters has failed to provide any protection against PE, and they have been associated with serious complications [57].

Neuraxial anaesthesia is contraindicated in pregnant women who receive anticoagulation once or twice daily at therapeutic doses. According to the current version of the European Society of Anaesthesiology (ESA) on neuraxial anaesthesia in patients receiving antithrombotic agents, the use of LMWH must be discontinued for at least 24 hours before puncture, and treatment can be resumed a minimum of 4 hours after catheter removal (Tab. IV) [58]. Spontaneous labour does not usually meet these time intervals, and the majority of anticoagulated women can therefore be expected to deliver without neuraxial anaesthesia. In women receiving UFH, heparin must be discontinued for at least 4–6 hours if it is administered intravenously and for at least 8–12 hours if it is administered subcutaneously before regional anaesthesia can be performed. UFH therapy can be restarted after a minimum of one hour after catheter removal or 4–6 hours after delivery if there are no bleeding complications. If the level of anticoagulation is uncertain, aPTT testing or, in cases of LMWH, assessment of aXa levels can be helpful. In cases where an emergency caesarean section is required, it will have to be performed under general anaesthesia.

Recommendation 5 – Upon the onset of labour or at least 24 hours before the induction of labour or a caesarean section, the administration of LMWHs should be discontinued. Neuraxial anaesthesia can be performed only after a minimum of 24 hours after a therapeutic dose of LMWH or at least 4-6 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.

Postpartum anticoagulation

Despite the inconvenience of subcutaneous injections, many women prefer to stay on LMWH therapy postpartum

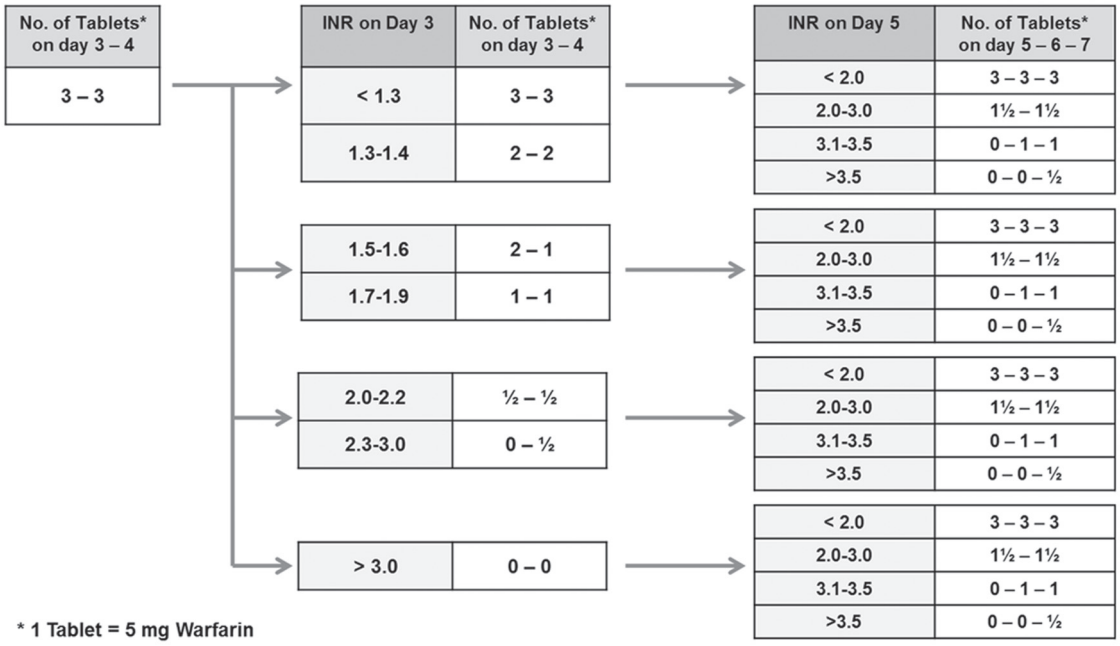

Figure 1. Nomogram for the initiation of warfarin therapy. According to the nomogram, 86 % of patients achieved the INR target range of 2.0 – 3.0 within 5 days [61].

because they have been accustomed to its administration and do not have to undergo regular INR monitoring while caring for the newborn [21]. Patel et al. investigated adherence to LMWH therapy antenatally and postnatally and observed a high mean percentage of adherence during the postpartum period that was only slightly lower than adherence in the antenatal period (i.e., 93.4 % and 97.9 %, respectively) [59].

Warfarin is an alternative to ongoing LMWH treatment, and patients can be switched to warfarin after postpartum vaginal bleeding has subsided [8, 11, 13]. The switch to warfarin requires an overlapping period with LMWH of approximately 5 days, with frequent INR monitoring. LMWH therapy can be terminated when the INR target range – generally 2.0-3.0 – has been achieved. A case-control study revealed that larger doses of warfarin and a longer time to reach the INR target range were required in postpartum women compared to non-pregnant women [60]. When switching to warfarin, dosing should commence using the anticipated maintenance dose or a dose based on nomograms [61, 62] (Fig. 1).

Both heparin and warfarin can be administered to breastfeeding women. In a case series of 15 women receiving LMWHs, small amounts of heparin were detected in the breast milk of 11 patients, but because neither UFH nor LMWH is orally active, no clinical effect would be anticipated in the infant [63]. Warfarin does not enter the breast milk in active forms and is considered safe for breastfeeding mothers. In contrast, phenprocoumon, which is more lipophilic than warfarin, is expected to be excreted into breast milk and is therefore not recommended [8, 64].

Recommendation 6 – Anticoagulant therapy in the postpartum period can be continued using LWMH or switched to warfarin with an overlapping phase and frequent INR monitoring.

Duration of VTE secondary prevention

No studies have addressed the issue of the optimal duration in anticoagulant therapies for pregnancy-associated VTE. Based on the evidence in non-pregnant patients and considering the high proportion of pregnant patients with proximal DVT and PE and the ongoing risk of VTE during the later stages of pregnancy and the postpartum period, the current guidelines recommend that anticoagulant therapy should be continued throughout pregnancy and for at least 6 weeks postpartum; they advocate a minimum total duration of therapy of 3 months [8, 13]. Patients should be monitored using regular ultrasound examinations of the venous system. In cases of delayed or absent recanalisation of the iliac or femoral veins, the patient should be considered to be at high risk for the development of a symptomatic post-thrombotic syndrome (PTS). These patients may benefit from prolongation of anticoagulant therapy.

Recommendation 7 – By extrapolating the recommendations of current guidelines for risk-associated VTE, we found that pregnant women with acute VTE should be anticoagulated for a minimum of 3 months, at least throughout pregnancy, and for 6 weeks postpartum.

Maternal risks of anticoagulation

Most Summaries of Product Characteristics (SmPC) for antithrombotic drugs are mainly based on the fact that these drugs have not been sufficiently tested during pregnancy and breastfeeding. For this and legal reasons, drugs are frequently considered to be contraindicated during

pregnancy and breastfeeding. The main risks for expectant mothers who are treated with heparins due to a venous thromboembolic event are VTE recurrence and the occurrence of bleeding complications, particularly during the peripartum period. However, heparins can cause additional side effects, such as pain and bruising at injection sites, allergic skin reactions, HIT and heparin-induced osteoporosis, when administered over the long-term.

Risk of VTE recurrence and bleeding

Evidence for VTE recurrence and bleeding risk in anticoagulated pregnant women is mainly derived from observational studies (Tab. V). A recent systemic review identified 18 studies that included 981 pregnant women with acute VTE. Of these patients, 822 (84%) were treated with LMWH, and the remainder were treated with UFH [4]. The incidence of major bleeding was 1.41% (95% CI 0.60-2.41%) antepartum and 1.90% (95% CI 0.80–3.60%) during the first 24 hours after delivery. Recurrent VTE during ongoing pregnancy occurred in 1.97% (95% CI 0.88–3.49%) of the patients. A previous systematic review investigated the outcomes of 2,777 pregnancies that included 174 women with acute VTE who were treated with LMWH at therapeutic doses [3]. Significant antepartum and postpartum bleeding occurred in 1.7% of women, and recurrent VTE was diagnosed in 1.2% of pregnant women. Nelson-Piercy et al. reported a higher overall maternal bleeding rate of 15.4% in a European retrospective multicentre trial that included 254 women who were treated with therapeutic doses of tinazparin [5]. There were no cases of fatal bleeding, but medical intervention due to severe bleeding was required in 3.4% of the cases. The safety and efficacy of LMWH for the treatment of VTE in pregnant patients has also been confirmed in other observational studies [26, 27, 65–68]. However, the number of women receiving therapeutic-dose LMWH in these studies was small; as a result of the retrospective study design, bleeding rates were potentially underestimated.

This risk of postpartum haemorrhage (PPH; i.e., blood loss >500 mL) has been observed to be approximately 5% within the first 24 hours after delivery, and occurred in 2% of women in the days following delivery [27]. Knol et al. assessed the risk of PPH in 88 patients who were treated with therapeutic doses of nadroparine and reported a 1.9-

Table V. Heparin treatment regimens for acute venous thromboembolism during pregnancy and outcomes

Study	Patients	Study Design	Treatment regimen	Outcome
Greer, 2005 (3)	174 acute VTE	Systematic review including 9 studies and 6 case reports	Enoxaparin (n = 105; 60%), Dalteparin (n = 49; 28%), Nadroparin (n = 20; 11%), Initial treatment with UFH in 20 cases (11%), Twice daily dosing in 153 cases (88%)	Recurrent VTE: 1.15% (95% CI, 0.14 – 4.09%) Significant bleeding (>500 mL): 1.72% (95% CI, 0.36 – 5.00%)
Voke, 2007 (27)	126 acute VTE	Multicenter observational study	Enoxaparin (n = 59; 47%), Dalteparin (n = 32; 25%), Tinzaparin (n = 31; 25%), Initial treatment with UFH in 16 cases (13%), Once daily dosing in 83 cases (66%), Switch from once → twice daily dosing antenatally in 10 cases (8%)	No recurrent VTE No antenatal major bleeding Major postpartum haemorrhage: 4.8%
Knight, 2008 (26)	143 antenatal PE, 259 controls	Multicentre case-control study	Treatment with LMWH (n = 134; 93.7%), Twice daily dosing in 68 cases (51%), Treatment with UFH (n = 6; 4%) 2 women died before treatment initiation	Recurrent PE: 1.4% (95% CI, 0.2 – 5.1%) No bleeding complications No thrombocytopenia No osteoporotic bone fractures Perinatal mortality: 4.4% (95% CI, 1.6 – 9.4%)
Nelson Piercy, 2011 (5)	254 acute VTE	Multicentre observational study	Tinzaparin (n = 254), Once daily dosing in 239 cases (94%), Last dose within 24 hours of delivery (34%)	Recurrent VTE: 1.97% (DVT: 0.39%; PE 1.57%) Antepartum bleeding: 3.6% Postpartum bleeding: 6.2%
Romualdi, 2013 (4)	981 acute VTE	Systematic review including 15 studies and 3 case reports	Initial treatment with LMWH (N = 822; 84%), Initial treatment with UFH (N = 159; 16%), 6 studies reported aXa-based LMWH dose adjustment	Recurrent VTE: 1.97% (95% CI, 0.88 – 3.49%) Recurrent PE: 1.30% (95% CI, 0.60 – 2.30) Antepartum major bleeding: 1.41% (95% CI, 0.60 – 2.41%) Major postpartum haemorrhage: 1.90% (95% CI, 0.80 – 3.60%)

Abbr.: DVT: Deep vein thrombosis, PE: Pulmonary embolism, VTE: Venous thromboembolism, LMWH: Low-molecular-weight heparin, UFH: Unfractionated heparin

fold increased risk of PPH; however, this did not result in an increase in the need for red blood cell transfusions. Moreover, the risk of severe PPH (i.e., blood loss > 1000 mL) after vaginal delivery was not increased. Severe PPH occurred in 5.6 % (4/71) of the cases and in 5.0 % (13/260) of the women not receiving anticoagulants (OR 1.1; 95 %-CI 0.4–3.6) [69]. The risk of PPH after caesarean section was 12 % (2/17) and 4 % (3/67), respectively, in women with and without anticoagulants. The risk of PPH was not substantially increased when women delivered within 12 to 24 hours after the last injection of LWMH [69, 70]. In comparison, the overall prevalence of PPH in European countries has been estimated to be approximately 6.4 %, and severe PPH is reported to occur in 1.8 % of all deliveries [71].

In a retrospective cohort study of 100 pregnancies in 77 UFH-treated women, the rate of major antepartum bleeding was 1 %, which was consistent with the bleeding rates reported to be associated with UFH and VKA therapy in non-pregnant patients [8, 72].

Heparin-induced thrombocytopenia

A serious adverse effect that has been attributed to the use of LMWH and UFH is HIT. Exposure to any kind of heparin may result in an autoimmune response that is characterised by the development of IgG antibodies directed against complexes containing heparin and platelet factor 4. The subsequent immune reaction results in thrombocytopenia and endothelial damage [73, 74]. HIT is characterised by a decrease in the platelet count of at least 50 %, an onset at 5–15 days after the initiation of heparin therapy and a prothrombotic state that places the patient at high risk for arterial and venous thrombotic complications [75]. It must be emphasised that thrombocytopenia resulting from other causes is not uncommon during pregnancy [76, 77], and pregnancy is generally classified as a low-risk condition for HIT. However, because HIT is a life-threatening complication that has been attributed to the use of heparins, the clinical suspicion of HIT requires the immediate discontinuation of therapy and a switch to a full-dose non-heparin anticoagulant treatment [48, 75].

The quality of evidence regarding the efficacy and safety of alternative anticoagulants during pregnancy is low. Lindhoff-Last et al. reviewed the use of danaparoid in 51 pregnancies in 49 patients identified in the literature between 1981 and 2004 [16]. Women were treated for a median duration of 10 weeks with danaparoid, either because of HIT (n = 32) or due to allergic skin reactions (n = 19). Danaparoid was administered until the delivery of a healthy child in 72 % of cases. In 21.6 % of cases, treatment had to be stopped earlier as a result of adverse events, and in 5.6 % of the cases, anticoagulant therapy was terminated because it was no longer required. Four cases of maternal bleeding complications were observed during the pregnancy or postpartum periods, two of which were fatal. No aXa activity was detected in 5 samples of foetal cord blood and 3 samples of maternal breast milk. Danaparoid can be considered as an alternative anticoagulant because it has been shown to be efficacious in cases of HIT and because it does not cross the placenta [78–81].

Elsaigh et al. reported on the use of fondaparinux in 13 women and 15 pregnancies [82]. Nine patients received treatment at therapeutic doses (7.5 or 10 mg/d), and six patients were treated with a lower prophylactic dose (2.5 or 5 mg/d). Only one woman experienced a recurrent VTE while on a full treatment dose. No major bleeding occurred during treatment with fondaparinux. The authors reported two cases of spontaneous pregnancy loss and one elective termination of pregnancy due to foetal anomalies (Fallot's tetralogy and Dandy-Walker syndrome). Case reports and small cohort studies reported no adverse outcomes when anticoagulant therapy was switched from heparin to fondaparinux, which occurred because of allergic skin reactions [15, 83–85]. On the basis of current evidence, the use of fondaparinux in cases of heparin intolerance seems to be well-tolerated and efficacious during pregnancy. However, there were no cases in which fondaparinux was used to treat HIT during pregnancy. At the present time, experience with fondaparinux during pregnancy is too limited to recommend fondaparinux over danaparoid in cases of suspected HIT.

Recommendation 8 – Heparin-induced thrombocytopenia in pregnant women is extremely rare. In pregnant women suspected of having HIT, consultation with a haemostaseologist or experienced thrombosis specialist is recommended to determine whether alternative anticoagulants, such as danaparoid or fondaparinux, are needed.

Heparin-induced allergic skin reactions

Heparin-induced skin reactions are primarily caused by delayed-type hypersensitivity (DTH; so-called type IV allergic reactions) [86]. DTH reactions to heparin are clearly more common than previously believed, and have been observed in up to 20 % of women who were treated with heparins throughout pregnancy [87]. Patients usually present with an itching erythema or red plaques at the sites of heparin injections. If an allergic skin reaction occurs during pregnancy, the most pragmatic option seems to be to switch to another heparin. However, the rate of cross-reactivity between heparins is high (33–73 %), and it has been shown that heparins with high molecular weight are more likely to induce allergic skin reactions [88]. In cases of several cross-reactions, treatment with an alternative anticoagulant, such as danaparoid or fondaparinux, may be considered.

Heparin-induced osteoporosis

Osteoporosis is a systemic skeletal disease that is characterised by a loss of mineral bone mass, alterations in bone microarchitecture and subsequent bone fragility that results in an increased risk of fractures. In particular, preg-

nant women are susceptible to osteoporosis when they are being treated with heparins for long periods of time (i.e., over several weeks or months) [8]. During pregnancy, the demand for calcium is increased, leading to the mobilisation of calcium and bone resorption. In some women, excessive resorption of mineral bone mass may occur. However, so-called pregnancy-associated osteoporosis is rare and thought to be multifactorial, and has been related to dietary factors (e.g., low calcium intake and vitamin D insufficiency) and to genetic factors (e.g., polymorphisms in the vitamin D or oestrogen receptor) [89]. The use of heparins may also increase the rate of bone resorption [90–93]. Osteopenia is caused by the binding of heparin to osteoclasts, which then release factors that activate osteoclasts in an interleukin 11-dependent fashion [94]. Heparin-associated osteoporotic fractures have been observed in 2-5% of patients treated with heparin for long periods of time. Both UFH and LMWH have the potential to produce osteopenia and increase the risk of bone fractures [95, 96]. However, the fracture risk is assumed to be substantially lower for LMWH, and this has been attributed to the lower affinity of LMWH to osteoblasts and osteoclasts [89, 97, 98]. Despite the existence of sporadic reports of symptomatic osteoporosis that occurs with the use of LMWH during pregnancy and postpartum [31, 99, 100], LWMH are considered at least as safe and effective as UFH, and have replaced UFH in most situations in which long-term treatment with heparin is indicated [3, 90]. Whether the use of prophylactic calcium supplementation in expecting mothers avoids heparin-induced osteopenia and lowers the risk of bone fractures has not yet been investigated.

Foetal risks of anticoagulation

Foetal safety is an important issue when considering the use of an anticoagulant therapy during pregnancy. Heparins do not cross the placenta and therefore have no impact on the risk of foetal bleeding [8, 101, 102]. There is also no evidence indicating that teratogenicity results from the use of LMWH or UFH during pregnancy [5, 65, 103]. Because it has a high molecular weight and a negative charge, UFH also does not appear in breast milk. However, small amounts of LMWH have been detected in the breast milk of women treated with prophylactic LMWH doses after caesarean section [63]. Because the bioavailability of orally administered heparins is negligible, traces of LMWH in the breast milk are considered harmless to the child [8, 104].

Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor that, like LMWH, exerts its actions via high-affinity reversible binding to antithrombin. Knol et al. observed no foetal haemorrhages or malformations in 12 pregnant women treated with 7.5 mg fondaparinux daily during pregnancy. However, in three of these women, severe PPH occurred, and in 2 of these cases, it occurred within 12 hours after the last injection [15]. In this context, the longer half-life of fondaparinux (i.e., 15–20 hours) compared to the half-life of LMWH (i.e., 3–6 hours) is a disadvantage, especially during the peripartum period [45]. Moreover, Dempfle reported that drug levels were one tenth of maternal levels in umbilical cord blood in aXa and aPTT assays [105]. Because there is a lack of appropriate data and because there is evidence for minor transplacental passage of fondaparinux, this substance is not recommended in pregnancy, and its use should be limited to patients with contraindications to heparins, such as heparin-induced skin reactions or thrombocytopenia [8, 14, 15]. In addition, it is unknown whether fondaparinux is secreted into human breast milk. However, fondaparinux has 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 [8].

VKAs cross the placenta, and coumarin exposure during the first trimester of pregnancy can result in severe foetal malformations [8]. Coumarin embryopathy is characteriSed by skeletal abnormalities, which include nasal hypoplasia, a depressed or narrowed nasal bridge, scoliosis, and calcifications in the vertebral column, femur, and heel bone that have a peculiar stippled appearance on X-rays. Limb abnormalities, such as brachydactyly or underdeveloped extremities, can also occur. In later pregnancy, coumarins increase the risk of pregnancy loss and foetal bleeding complications. Common non-skeletal features include low birth weight and developmental disabilities. The use of warfarin throughout pregnancy is associated with a congenital anomaly rate of 3.7–6.4% [106, 107]. In a European prospective multicentre study that included 666 pregnant women exposed to VKA, only two coumarin embryopathies were observed in the women exposed to phenprocoumon during the first trimester, resulting in an incidence rate of 0.6% [108]. Because they have the potential to harm the foetus, the use of VKA to treat uncomplicated pregnancy-associated VTE cannot be recommended.

Warfarin and acenocoumraol can be prescribed to lactating women. Because both molecules are polar, non-lipophilic and highly protein-bound, they are not expected to appear in significant amounts in breast milk [8, 64]. In contrast, concerns have been raised regarding the use of the less polar, more lipophilic VKA, such as phenprocoumon, which might be excreted into breast milk and should therefore be avoided in breast-feeding women.

Pregnant and breast-feeding women were excluded from trials evaluating new oral direct thrombin and factor Xa inhibitors. Because these drugs are relatively small molecules, they are thought to cross the placental barrier, and should therefore be avoided during pregnancy [17, 109]. The teratogenicity of dabigatran and rivaroxaban has been described in animal studies [8, 17, 20]. Rivaroxaban has also been reported to be secreted into breast milk. Therefore, the manufacturers of dabigatran and rivaroxaban both recommend against using these medications in breast-feeding women.

Therapeutic options in life-threatening PE

Thrombolytic therapy

The maternal and foetal risks of thrombolytic therapy have not been adequately studied. Although recombinant tissue plasminogen activator (rt-PA) and streptokinase are large molecules, minimal transplacental passage has been demonstrated for these drugs, and there are therefore concerns about severe adverse effects, such as bleeding complications, pregnancy loss, premature labour and placental abruption [110–112]. The maternal risk of bleeding, mostly from the genital tract, has been described to be approximately 6–8%, which is consistent with the risk in non-pregnant patients receiving thrombolytic therapy [11]. A 6% rate of foetal loss and a 6% rate of pre-term delivery have been reported [110]. However, the overall number of cases with successful systemic thrombolysis in pregnancy is small, and a publication bias resulting from a predominance of cases with a favourable outcome must be taken into account. The treatment of VTE using systemic thrombolysis must therefore be regarded as relatively contraindicated during pregnancy and in the peripartum period, and should be reserved for life-threatening cases of PE [1, 8, 9, 11].

UFH is recommended as the initial anticoagulant in patients with suspected PE and haemodynamic compromise (e.g., hypotension, tachycardia, refractory hypoxaemia, collapse or shock) because of its rapid effect and short half-life, which allow for dose-adjustment, especially if thrombolysis is considered [1, 9, 13]. After haemodynamic stabilisation, therapy can be switched to LMWH. In the case of systemic thrombolysis, it has been recommended to omit the UFH loading dose and start infusion at a rate of 18 U/kg/h in parallel with or after the administration of the thrombolytic agent [9]. If the patient is not suitable for thrombolysis or if thrombolysis has failed, catheter-assisted endovascular or surgical embolectomy must be considered. The decision regarding which method should be applied depends on the local expertise and available resources.

Recommendation 9 – Systemic thrombolysis in pregnancy should only be considered in life-threatening PE because of possible maternal and foetal risks.

Inferior vena cava filters

In the recently published PREPIC-2 trial, the addition of the insertion of a retrievable IVC filter for 3 months to anticoagulant therapy provided no benefit in terms of PE recurrence or mortality in non-pregnant patients presenting with acute symptomatic PE [57]. Therefore, filter insertion into the IVC in pregnant women treated with anticoagulants cannot be recommended and should be restricted to women with severe contraindications against anticoagulant therapy or in those with recurrent PE despite adequate anticoagulation. Temporary filter placement may also be considered in the peripartum period if acute iliofemoral DVT occurs after the 36th week of gestation. Because their use in pregnant women is limited to case reports or small case series, it remains uncertain whether they are beneficial in this setting [113–116]. Each case requires individual assessment, and the risks of filter placement and complications, such as filter migration (20% of cases), filter fracture (5% of cases) and filter perforation (up to 5% of cases), has to be considered. In addition, the radiation time required for filter placement must be considered. According to the literature, a radiation time <2 minutes is estimated, which will yield a radiation dose <5 mSv with abdominal shielding [117].

Recommendation 10 – The use of IVC filters is not recommen-ded in pregnancy-associated VTE unless recurrent PE occurs despite adequate anticoagulation or when severe contrain-dications to anticoagulant therapy exist.

Therapeutic options in limb-threatening DVT

A delay or failure of venous recanalisation, in particular if the iliac or femoral veins remain occluded, has been identified as a substantial risk factor for the development of drome (PTS). In non-pregnant patients, strategies involving early thrombus removal using either endovascular or surgical techniques must be considered [118]. It remains unclear whether these treatment options are also a safe and effective alternative in pregnant women. In a case series, Herrera et al. presented outcome data for 13 pregnant women with extensive DVT involving the iliofemoral veins who were treated with catheter-directed or pharmacomechanical thrombolysis (n=11) or surgical (n=2) venous thrombectomy [119]. After a mean follow-up of 1.3 years (range 1–74 months), venous duplex ultrasound revealed patent veins in 12/13 patients (92%) and normal valve functions in 10/13 patients (77%). In 11/13 patients (85%), Villalta scores were <5, indicating no relevant post-thrombotic sequelae. Concerns have been raised regarding radiation doses ranging between 55 and 450 mGy and the risk of complications, such as major bleeding with the need for transfusion (n=2), puncture site haematoma (n=3) and popliteal artery pseudoaneurysm (n=1). The risks and benefits of these invasive techniques should be assessed in further prospective studies.

Recommendation 11 – Because outcome data regarding early thrombus removal strategies in cases of extensive DVT are sparse, endovascular or surgical thrombectomy should only be considered for limb-threatening DVT (i.e., phlegmasia coerulea dolens). Thus, for the large majority of cases with pregnancy-associated VTE, anticoagulant therapy alone remains the treatment option of choice.

Long-term outcomes after pregnancy-associated VTE

Post-thrombotic syndrome

Because pregnancy-associated DVT often involves the iliac and femoral veins, a substantial number of women are thought to develop long-term sequelae following extensive DVT. In a sub-analysis from the Home-LITE study, Hull et al. compared the long-term use of tinzaparin (i.e., for more than 12 weeks) versus the administration of tinzaparin for 5 days followed by warfarin for 12 weeks in patients with proximal DVT, and reported a lower frequency of PTS in patients who received prolonged treatment with LMWH [120]. The benefits of a prolonged LMWH therapy were even greater for iliac vein thrombosis than for DVT not involving the iliac veins. Although this study was conducted in non-pregnant patients, the results may be relevant to pregnancy-associated DVT because iliac vein thrombosis is more common during pregnancy, and favourable effects from long-term LMWH treatment during pregnancy can therefore be expected. Clinical data related to long-term outcomes after pregnancy-associated VTE are scarce. The typical symptoms of PTS are persistent leg swelling, pain, cramps, heaviness, paraesthesia, hyperpigmentation, venous ectasia, and sometimes overt ulcers that can develop months or years after the acute thrombotic event. In non-pregnant patients, PTS is associated with a substantially increased risk for VTE recurrence. Outside pregnancy, the clinical symptoms of PTS persist in 25–50 % of cases after DVT, and severe PTS has been reported to occur in approximately 5–10 % of cases [121]. Comparable outcomes have been observed for pregnancy-associated DVT. In a long-term follow-up over 3–16 years, women with pregnancy-associated DVT developed any degree of PTS in 42 % of cases and severe PTS in 7 % of cases, with postnatal proximal DVT being the strongest risk factor for PTS (OR 6.3; 95 % CI 2.0–19.8) [122].

Compression therapy

In the case of DVT and pronounced swelling in a lower limb, leg elevation and compression bandages should be used during the acute phase to reduce pain and oedema.

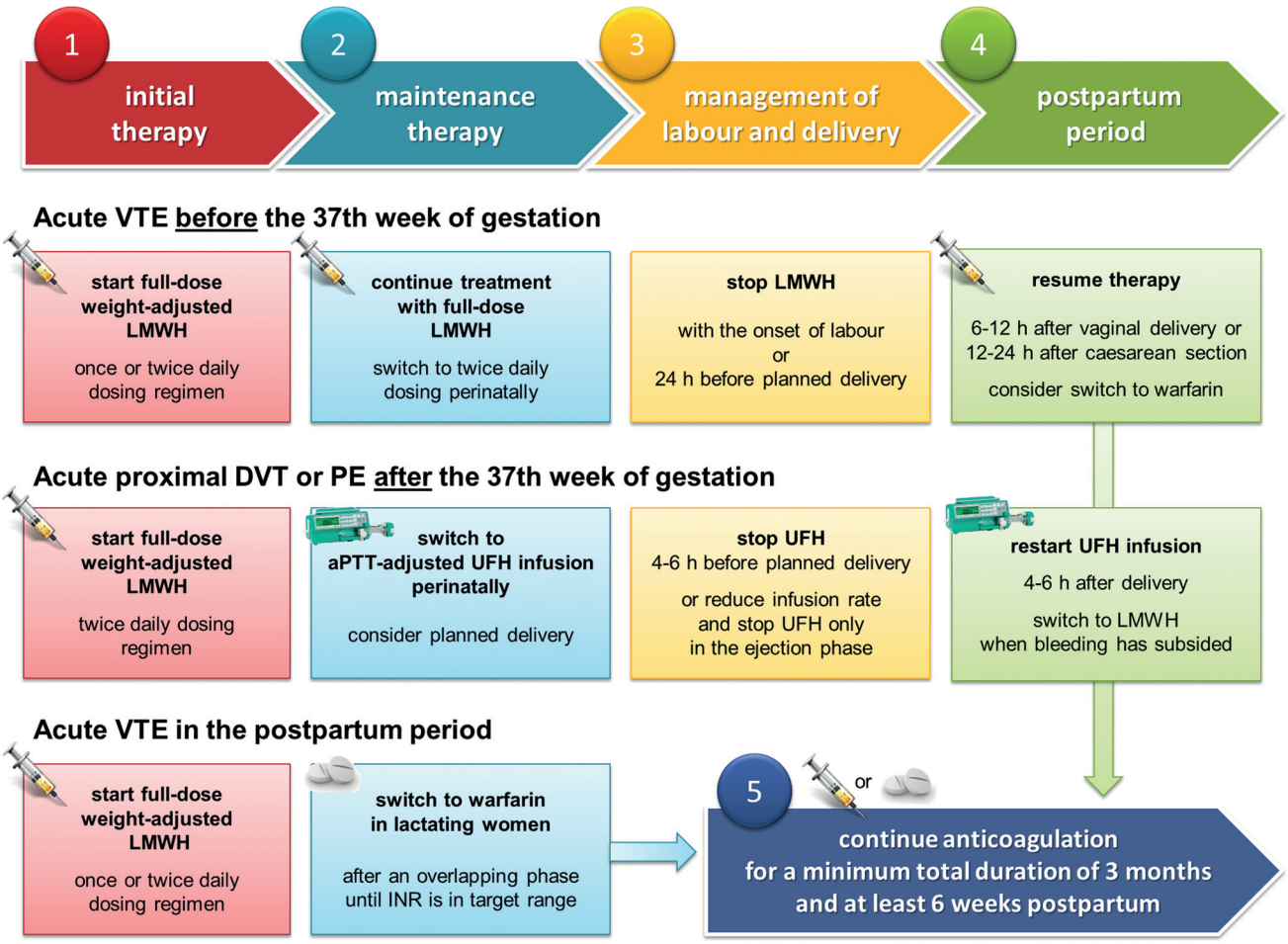

Figure 2. Suggested approach for the management of anticoagulant therapy during pregnancy and the perinatal period.
Abbr.: DVT: Deep vein thrombosis, PE: Pulmonary embolism, VTE: Venous thromboembolism, LMWH: Low-molecular-weight heparin, UFH: Unfractionated heparin.

Whenever possible, the woman should be kept mobilised along with compression therapy, which is recommended to be continued with fitted graduated elastic compression stockings (GCS; class 2, corresponding to a pressure of 23-32 mmHg) as soon as the leg swelling declines. Data from trials performed in non-pregnant patients suggest that the incidence of PTS can be reduced by 50 % if compression therapy is continued for two years [9]. In contrast, the recently published placebo-controlled SOX study was unable to confirm beneficial effects of compression therapy on the incidence of PTS, but this may be the result of a low compliance rate (i.e., 55.6 %) [123]. Because of weaknesses in the design of this study, current German guidelines continue to recommend compression treatment [21]. There is no doubt that GCS improves symptoms in patients by reducing pain and leg swelling [124]. Furthermore, GCS were shown to reduce venous vessel diameters and increase blood flow velocity in the common femoral vein in postpartal DVT, which can reduce venous stasis and may improve venous function in the long-term [125].

Recommendation 12 – Compression therapy involving the use of compression bandages or graduated compression stockings is recommended, at least throughout pregnancy and the postpartum period because this relieves symptoms during the early phase and prevents later sequelae such as PTS. Based on data from non-pregnant populations, compression therapy after proximal DVT should be continued for at least 2 years and longer if symptoms of PTS persist.

Conclusions

Because there is a lack of adequate study data, management strategies for pregnancy-associated VTE must be deduced from small observational studies and extrapolated from recommendations for non-pregnant patients. On the basis of current evidence, weight-adjusted, full-dose LMWH is the anticoagulant treatment of choice during pregnancy. A once or twice daily LMWH dosing regimen is possible, but a twice daily dosing regimen seems to be advisable, at least perinatally. It remains unclear whether adjusting doses according to factor Xa activity provides any benefit. The management of delivery deserves special care and attention and depends on the time interval between the diagnosis of VTE and the expected delivery date. In particular, if VTE manifests at term, delivery should be attended by an experienced multidisciplinary team. The different anticoagulant management strategies currently in use are summarised in Figure 2. We conclude that there is an urgent need for well-designed prospective studies to compare different management strategies in women with pregnancy-associated VTE.

Abbreviations

aPTT	Activated partial thromboplastin time
aXa	Anti-factor Xa level
BNP	Brain natriuretic peptide
DTH	Delayed-type hypersensitivity
DVT	Deep venous thrombosis
GCS	Graduated compression stockings
HIT	Heparin-induced thrombocytopenia
LMWH	Low molecular weight heparin
NOAC	Novel oral anticoagulant
PE	Pulmonary embolism
PPH	Postpartum haemorrhage
PTS	Post-thrombotic syndrome
rt-PA	Recombinant tissue plasminogen activator
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

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