How Do We Treat Pregnancy-Related Venous Thromboembolism?

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Hämostaseologie

Abstract

Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality during pregnancy and the postpartum period. Due to a lack of adequate study data, therapeutic strategies for pregnancy-related VTE are deduced from observational studies and extrapolated from recommendations for nonpregnant patients. Because heparins do not cross the placenta, weight-adjusted therapeutic-dose low-molecular-weight heparins (LMWHs) are the anticoagulant treatment of choice in cases of VTE during pregnancy. Once- and twice-daily dosing regimens are suitable. There is no evidence that measurement of factor Xa activities and consecutive LMWH dose adjustments improve clinical outcomes. There is no support for the routine use of vitamin K antagonists, direct oral thrombin or factor Xa inhibitors, fondaparinux, or danaparoid in uncomplicated pregnancy-related VTE. Management of delivery deserves special attention, and treatment strategies depend on the time interval between the diagnosis of acute VTE and the expected delivery date. 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.

Keywords

- venous thromboembolism
- deep vein thrombosis
- pulmonary embolism
- heparin
- pregnancy
- postpartum

Zusammenfassung

Venöse Thromboembolien (VTE) sind eine der Hauptursachen für mütterliche Morbidität und Mortalität während der Schwangerschaft und postpartal. Aufgrund fehlender randomisierter kontrollierter Studien sind therpeutische Strategien vorzugsweise aus Beobachtungsstudien und aus Therapieempfehlungen für Nicht-Schwangere abgeleitet. Heparine sind nicht plazentagängig und gelten in der Schwangerschaft als sicher. Niedermolekulare Heparine (NMH) in gewichts-adaptierter volltherapeutischer Dosierung sind daher Mittel der Wahl für die VTE-Therapie in der Schwangerschaft. Dosisregime mit Einmal- oder Zweimalgabe sind möglich. In Abhängigkeit des Präparates wird das NMH ein- oder zweimal täglich subkutan appliziert. Da es keine Evidenz für einen Nutzen einer Dosisanpassung an anti-Faktor-Xa-Spiegel gibt, werden routinemäßige Spiegelkontrollen nicht empfohlen. Andere Antikoagulanzien wie Vitamin-K-

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Schlüsselwörter
- venöse Thromboembolie
- tiefe Venenthrombose
- Lungenembolie
- Heparin

Antagonisten, die direkten oralen Thrombin- und Faktor-Xa-Inhibitoren (DOAKs), Fondaparinux und Danaparoid haben in der VTE-Behandlung bei unkompliziertem Schwangerschaftsverlauf keinen Stellenwert. Das peripartale Vorgehen hängt wesentlich vom Zeitabstand zwischen VTE-Manifestation und dem Geburtszeitpunkt ab. In der Stillzeit kann die NMH-Therapie fortgeführt oder überlappend auf Warfarin umgestellt werden. Bei schwangerschafts-assoziierter VTE sollte eine Antikoagulation für die Mindestdauer von 3 Monaten und bis mindestens 6 Wochen postpartum fortgeführt werden.

Introduction

Venous thromboembolism (VTE) complicates approximately 1 to 2 of 1,000 pregnancies. The risk is higher in women with previous VTE events, known hereditary or acquired thrombophilia, and those with a positive family history of VTE. The risk increases further with increased age, obesity, the presence of concomitant diseases (e.g., hypertensive disorders of pregnancy, ovarian hyperstimulation syndrome), and delivery by caesarean section.[1,2] Approximately 80% of pregnancy-related VTE manifest as symptoms of deep vein thrombosis (DVT), whereas the remaining 20% are pulmonary embolisms (PEs) or a combination of DVT and PE. Of note, PE is a leading cause of maternal morbidity in the Western world. The risk of VTE is approximately fivefold increased during pregnancy compared with age-matched nonpregnant women. There is a steady risk increase in the course of pregnancy with a peak at term. After delivery, the elevated risk of thrombotic events remains high for the first 6 weeks postpartum and is no longer increased beyond 12 weeks.[3]

Diagnosis of Pregnancy-Related VTE

It is emphasized that clinical prediction rules currently in use for the diagnosis of VTE in nonpregnant patients (e.g., Wells score) have not been prospectively validated in pregnancy or in the postpartum period. Furthermore, D-dimers physiologically increase throughout pregnancy and peak at delivery. Thus, a negative D-dimer test result based on the reference values of nonpregnant patients becomes unlikely in the second and third trimesters. Trimester-specific reference intervals have been suggested but vary based on the assay used; these intervals have not been validated to date in prospective studies.[4] Imaging studies therefore play a major role in confirming suspected DVT or PE in pregnant women. Combined modality ultrasound, i.e., complete compression ultrasound of the lower extremity veins and duplex ultrasound of the iliac veins, is the method of choice for diagnosing DVT during pregnancy and postpartum. For the confirmation of clinically important central and segmental emboli in the lungs, computed tomography pulmonary angiography (CTPA) and lung scintigraphy are recommended.[2,5,6] Fetal radiation exposure and contrast-related side effects remain major concerns, but it must be emphasized that radiologic imaging can be used in pregnancy as long as pregnancy-adapted protocols are used to achieve the lowest radiation doses possible. All imaging techniques show pregnancy-specific limitations. For further details concerning the diagnostic strategy of pregnancy-related VTE, we refer to a recently published systematic review.[2] Only recently, van der Pol et al suggested that determining a pregnancy-modified YEARS algorithm can safely rule out PE without the use of CTPA.[7] In a prospective study involving pregnant women suspected of PE, three criteria of the YEARS algorithm (i.e., clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis) were assessed and D-dimer levels were determined. PE was ruled out if one or more of the three criteria were met and D-dimer levels were less than 500 ng/mL or if none of the three criteria were met and D-dimer levels were less than 1,000 ng/mL. According to this algorithm, CT angiography was avoided in 39% (95% confidence interval [CI]: 35–44), thus averting potential harm from radiation to the fetus.

Initiation of Therapy

Before anticoagulant therapy is started, the following tests are recommended to exclude severe coagulation disorders and renal or hepatic dysfunction: complete blood cell counts, prothrombin time, activated partial thromboplastin time (aPTT), renal and liver function tests, and electrolytes. In women with a high clinical suspicion or confirmed VTE, treatment with parenteral anticoagulants should be started immediately while awaiting laboratory test results. Because the risk of developing heparin-induced thrombocytopenia (HIT) in uncomplicated pregnancy is thought to be very low (i.e., less than 0.1%), current guidelines do not advocate routine platelet count monitoring for these patients.[8,9] However, platelet count monitoring every 2 to 3 days between days 4 and 14 should be performed in pregnant women who are postoperative or who receive unfractionated heparin (UFH) for more than 5 days.

In the case of acute DVT and pronounced swelling in a lower limb, leg elevation and compression bandages should be used to reduce pain and edema. Whenever possible, the woman should be kept mobilized along with compression therapy, which is recommended to be continued with fitted graduated elastic compression stockings (class 2, corresponding to a pressure of 23–32 mm Hg) as soon as leg swelling is reduced. Patients should be instructed to wear the stockings every day during ambulant hours. The

incidence of postthrombotic syndrome (PTS) after proximal DVT can be reduced by 40 to 50% if compression therapy is consistently continued for up to 2 years.[10,11] Only recently, the IDEAL-DVT study performed in nonpregnant patients demonstrated that an individualized therapy with compression stockings according to patients' symptoms was noninferior to standard duration therapy of 24 months.[11]

Treatment of VTE during pregnancy and postpartum should take into account the safety of both the mother and the child. Pregnant women who present with acute proximal DVT or PE are generally admitted to the hospital. For cases with low-risk VTE, it is likely that early discharge and outpatient therapy are as beneficial as hospital-based treatment.[6,12,13] However, when treated as outpatients, pregnant women should be followed closely.

Anticoagulation during Pregnancy

It is emphasized that pregnant women have been excluded from all major randomized controlled trials that have investigated the efficacy and safety of different anticoagulant regimens. Heparins do not cross the placenta barrier and do not appear in breast milk in significant amounts. They are therefore the pharmacologic agents of choice for the treatment of pregnancy-related VTE. In general, subcutaneously administered full-dose weight-adjusted low-molecular-weight heparin (LMWH) is preferred over UFH.[6,14] Once- or twice-daily dosing regimens are acceptable for the treatment of acute VTE during pregnancy (►Table 1).

Numerous observational studies and three systematic reviews have confirmed efficacy and safety of LMWH.[14–16] One review including 981 pregnant women with acute VTE reported VTE recurrence during on-going pregnancy in 1 to 2%, whereas major bleeding occurred in 1.4% antepartum and 1.9% postpartum.[15] The risk of postpartum hemorrhage (blood loss > 500 mL) is highest within the first 24 hours after delivery, and a 5 to 10% risk has been reported for women with therapeutic doses of LMWH.[17,18] Of note, the overall prevalence of postpartum hemorrhage (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.[19] Nelson-Piercy et al reported a higher overall maternal bleeding rate of 15.4% in a European retrospective multicenter trial that included 254 pregnant women who were treated with therapeutic doses of tinzaparin. Among patients who received the last injection within the previous 24 hours (median time interval 12.9 hours), 13.5% had a blood loss at delivery of 500 to 1,000 mL, and 0.4% suffered a blood loss >1,000 mL. There were no cases of fatal bleeding, but medical intervention due to severe bleeding was required in 3.4% of the cases.[20]

Table 1 Low-molecular-weight heparins—full therapeutic dosing regimens

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

Abbreviation: s.c., subcutaneous.
[a]A once daily dosing regimen is not licensed in some countries.

Unresolved Questions

First, it is unclear whether prepregnancy *weight* should be used to determine the appropriate dose of LMWH or whether dose adjustments are required as the pregnancy progresses and body weight increases.[17] However, after delivery, the LMWH dose should be adjusted to the postpartum weight of the woman because supratherapeutic levels of LMWH have been observed when the antenatal dose was continued postpartum.[21]

Second, it is unknown whether therapeutic LMWH regimens with *once-daily and twice-daily injections* differ in terms of efficacy and safety. It has been suggested that a twice-daily regimen may be superior to once-daily dosing given lower peak levels and an assumed lower bleeding risk.[22,23] Given changes in the pharmacokinetic profile of LMWH during pregnancy (e.g., increase of the glomerular filtration rate, increase of the plasma volume, and the apparent distribution volume), effects are difficult to predict. However, no difference in clinical outcomes has been observed in observational studies between women using once-daily or twice-daily regimens throughout pregnancy.[12,24] A Cochrane review including 1,508 nonpregnant patients also revealed no statistically significant difference between the two treatment regimens in terms of VTE recurrence, major bleeding, improvement of thrombus size, or mortality.[25] Thus, both once-daily and twice-daily LMWH regimens seem to be suitable for the treatment of acute VTE during pregnancy.

Third, whether it is useful to measure *anti-factor Xa (aXa) levels* with consecutive LMWH dose adjustments remains a controversial issue. Studies of various LMWHs in pregnant women have shown conflicting results.[14] An optimal aXa target range during pregnancy has not been determined. Studies investigating the pharmacologic profile of LMWH during pregnancy revealed a decrease in peak aXa levels and an increase in trough aXa levels with the progression of pregnancy.[26,27] Due to substantial interassay and interlaboratory variability in aXa measurements in patients treated with therapeutic-dose LMWH, the validity of using peak aXa levels as a marker of antithrombotic activity has been questioned.[28–30] Moreover, 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.[31] According to current evidence, routine aXa monitoring is therefore not generally recommended during pregnancy.[6,14,32,33] Similar to nonpregnant patients, aXa monitoring can be considered in obese or underweight women (i.e., <50 or >100 kg) in cases with severe renal impairment and those supposed to be at high risk for recurrent VTE or bleeding. Monitoring of aXa levels is recommended in situations of VTE progression to differentiate between underexposure to LMWH, which requires dose escalation or switching to an alternative, and

noncompliance which requires patient education. Because heparins exert their activity by binding to antithrombin, their anticoagulant effect may be attenuated in antithrombin-deficient women. Monitoring aXa levels and adjusting heparin doses to achieve adequate aXa levels are recommended for these cases. Supratherapeutic doses or the coadministration of antithrombin may be required. According to the current American College of Chest Physicians (ACCP) guideline, 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).[34]

Fourth, the optimal *intensity of anticoagulation* is an issue that has been addressed mainly in the nonpregnant population. A reduction to 75% of full-therapeutic-dose LMWH has been successfully established in patients with malignancy-associated VTE who are treated over several months or in the long-term with dalteparin.[35] Whether a comparable strategy is also safe in pregnant women is uncertain but may be desirable to minimize the risk of bleeding complications, particularly at term. Among 66 pregnant women with acute VTE included in the Efficacy of Thromboprophylaxis as an Intervention during Gravidity (ETHIG) study, no recurrent events were observed after dose reduction to 50 to 75% of the full therapeutic dose from the third week onwards.[36] In a systematic review including 152 women with pregnancy-related VTE who were treated with intermediate-dose LMWH during on-going pregnancy after the acute treatment phase, Gándara et al identified only one recurrent DVT that occurred when a 50% dose reduction was performed within 7 days after the initial diagnosis of DVT.[37] Of note, the studies included in this review were not intended to answer the question of optimal LMWH dosing to prevent recurrent VTE. However, the use of intermediate doses of LMWH may be an alternative if limited venous thrombosis occurs during early pregnancy in association with transient risk factors other than pregnancy (e.g., distal DVT or limited superficial vein thrombosis following transient immobilization).

Finally, the optimal *duration of anticoagulant therapy* after pregnancy-related VTE has not been determined. By extrapolating current guideline recommendations for risk-associated VTE, we found that pregnant women with acute VTE should be anticoagulated for a minimum duration of 3 months, at least throughout pregnancy, and for 6 weeks postpartum.[14,32,33] In cases of delayed or absent recanalization of the iliac or femoral veins, the patient should be considered to be at high risk for the development of a symptomatic PTS. These patients may benefit from prolongation of anticoagulant therapy for 6 to 12 months.

Side Effects of Heparin Therapy

Heparin-induced skin reactions are mainly delayed-type IV hypersensitivity (DTH) reactions at the sites of heparin injections. DTH reactions to heparin have been observed in up to 20% of women who were treated with heparins throughout pregnancy. The most pragmatic therapeutic approach is to switch to another heparin. Of note, the rate of cross-reactivity between heparins is high (33–73%).[38,39] In cases of several cross-reactions, treatment with an alternative anticoagulant, such as danaparoid or fondaparinux, may be considered.

Heparin-induced thrombocytopenia. Exposure to any type of heparin may result in an autoimmune response that is characterized by the development of IgG antibodies directed against complexes containing heparin and platelet factor 4.[40] The subsequent immune reaction results in a decrease of platelets of at least 50% that typically occurs at 5 to 15 days after the initiation of heparin therapy and places the patient at high risk for arterial and venous thrombotic complications. It must be emphasized that thrombocytopenia from other causes is not uncommon during pregnancy,[41] and pregnancy is generally considered as a low-risk condition for HIT. Incidence rates of $<0.1\%$ have been reported for LMWH, and the risk is higher if pregnant women are postoperative or have been exposed to UFH (0.1–1%). However, because HIT is a life-threatening complication, clinical suspicion of HIT requires immediate discontinuation of therapy and a switch to a full-dose nonheparin anticoagulant.[8]

Heparin-associated osteoporotic fractures have been observed in 2 to 5% of patients treated with UFH for long-term periods of time.[42,43] The fracture risk was assumed to be substantially lower for LMWH, which has been attributed to the lower affinity of LMWH to osteoblasts and osteoclasts.[44] A recent study investigated the bone mineral density (BMD) by dual-energy X-ray absorptiometry (DEXA) 4 to 7 years after the last delivery in 152 women. No osteoporosis or osteoporotic fractures were observed, and there was no evidence for a decrease in BMD in the 92 women with long-term use of LMWH during pregnancy compared with women who were not exposed to heparins.[45]

Alternative Anticoagulants

UFH is an alternative to LMWH that has a shorter half-life (i.e., 1–2 hours) and can be counteracted by protamine sulfate. Physiologically, it is cleared from blood by the reticuloendothelial system and endothelial cells and by renal excretion. Thus, UFH may be advantageous over LMWH in women at high risk for bleeding or those with severely impaired renal function. In addition, women with confirmed PE and hemodynamic compromise who are candidates for subsequent thrombolysis should also receive UFH during the initial phase until definitive treatment decisions are taken.[46] Treatment with UFH at therapeutic doses requires aPTT monitoring to achieve a 1.5- to 2.5-fold prolongation of the aPTT and an aPTT level that corresponds to an aXa level of 0.3 to 0.7 U/mL.[34] UFH can also be administered subcutaneously through twice-daily injections. In cases of subcutaneous administration, aPTT tests should be performed at 5 to 6 hours after injection to assure a therapeutic prolongation. Because the aPTT response to UFH is often attenuated during pregnancy, higher heparin doses may be required to obtain aPTT values in the therapeutic range.[46–48] Of note, compared with LMWH, UFH is associated with a substantially higher risk of adverse side effects, such as HIT, hemorrhage, allergic skin reactions, and osteoporosis.[49,50]

Fondaparinux and danaparoid are therapeutic options if heparins are contraindicated due to adverse side effects (e.g., heparin-induced skin lesions, HIT). Of note, experience with the use of these anticoagulants during pregnancy is limited.[51–53] Some placental transfer with fondaparinux has been reported,[54] and it is unknown whether fondaparinux is secreted into human breast milk. If HIT is suspected or confirmed in a pregnant woman, danaparoid can be preferred over fondaparinux because the heparinoid does not cross the placenta; in addition, the heparinoid is efficacious in cases of HIT, whereas experience with fondaparinux during pregnancy-associated HIT is too limited.[52] The longer half-life of fondaparinux (i.e., 15–20 hours) and danaparoid (i.e., ≈24 hours) must be considered at term.

Vitamin K antagonists (VKAs) cross the placenta and have the potential to cause both teratogenicity and fetal bleeding. Women exposed to VKA between the 6th and 12th weeks of gestation are supposed to have a 2 to 7% risk to develop coumarin embryopathy, which is characterized by skeletal abnormalities, including facial dysplasia, scoliosis, limb abnormalities, and calcifications in the vertebral column, femur, and heel bone that have a peculiar stippled appearance on X-rays.[55,56] In later pregnancy, VKAs increase the risk of pregnancy loss and fetal bleeding. Common nonskeletal features include low birth weight and developmental disabilities. VKAs are therefore not recommended for women with pregnancy-related VTE.

Direct oral anticoagulants (DOACs) are relatively small molecules that are able to cross the placenta barrier.[57–59] Thus, they have the potential to exert anticoagulant effects to the fetus and are also thought to be secreted into breast milk.[60,61] Animal studies of dabigatran and rivaroxaban revealed that they caused teratogenic effects, placental abnormalities, and fetal hemorrhage and reduced fetal viability. However, a recent review of cases with DOAC exposure in pregnancy revealed that DOACs might not carry a high risk of embryopathy and their effects to human fetuses remains largely unknown.[60] DOACs are therefore contraindicated during pregnancy or lactation.[62–65]

Follow-Up during the Course of Pregnancy

There are no data from clinical trials demonstrating that an intensified follow-up strategy of pregnant women with VTE improves clinical outcomes. However, because the risk of thrombus propagation and VTE recurrence within the first weeks of treatment remains increased, it should be common practice to schedule close clinical (in the case of PE) and imaging (in the case of DVT) follow-up especially in the initial phase of therapy to detect worsening of symptoms, clot extension, and drug side effects such as allergic reactions at heparin injection sites. The follow-up schedule practiced in our institution is presented in ►Table 2.

Table 2 Follow-up checklist after pregnancy-related VTE

	Items	Time intervals or conditions
Check regularly	***Worsening of clinical symptoms?*** → Leg pain or swelling? → Chest pain, dyspnea, or cough with bloody-streaked sputum? ***Thrombus extension?*** → Venous ultrasound examination ***Adherence to therapy?*** → LWMH injections? Drug prescription and coverage? Compression stockings? ***Drug side effects?*** → Allergic reactions at heparin injection sites? ***Routine blood parameters?*** → Blood cell count, renal, and liver function tests	Day 7 and 14 after discharge, then every 6 weeks and in cases of clinical deterioration
Consider	***Platelet count monitoring*** (every 2–3 days between day 4 and 14)	If the risk of heparin-induced thrombocytopenia (HIT) exceeds 1%, i.e., in cases of UFH therapy or after major surgery
	Anti-factor-Xa monitoring (2–4 hours after subcutaneous injection)	At extremes of body weight, in cases of severe renal impairment, progressive or recurrent VTE, high risk of recurrent VTE or bleeding complications, antithrombin deficiency
	De-escalation of anticoagulant therapy possible?	In cases of limited venous thrombosis when the risk of recurrent DVT and PE is considered low or if the risk of bleeding is high

Abbreviations: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

Management of Delivery

The options for delivery should be assessed at an early stage by a multidisciplinary team. Generally, spontaneous or induced vaginal delivery remains the preferred mode of delivery in women who are anticoagulated due to pregnancy-related VTE. 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 therefore be reserved mainly for patients with obstetric indications.[14,15] It is important to advise anticoagulated women early to pause LMWH as soon as labor starts, which is indicated by contractions or the rupture of membranes. Although it is uncertain whether twice-daily LMWH regimens are attended by a lower bleeding risk than once-daily dosing, some authors advocate switching to a twice-daily dosing regimen perinatally because this may avoid high aXa levels at the time of delivery.[14] This approach is advisable at least for women who are at high risk for postpartum hemorrhage. Of note, the main causes of primary postpartum hemorrhage are uterine atony and trauma, and LMWH presumably does not predispose the patient to atonic uterine bleeding.[6,66] According to the current version of the European Society of Anaesthesiology (ESA) on neuraxial anesthesia in patients receiving antithrombotic agents, LMWH must be discontinued for at least 24 hours before puncture (►Table 3).[67] Spontaneous labor usually does not meet these time intervals, and women should be instructed that they will not be able to receive neuraxial anesthesia and that an emergency caesarean section, if necessary, will have to be performed under general anesthesia.

The optimal time to restart anticoagulation postpartum has not been determined. In general, anticoagulant therapy should be restarted no sooner than 6 to 12 hours after vaginal delivery and 12 to 24 hours after caesarean section, depending on the amount of blood loss and the anticipated risk of recurrent VTE in the absence of anticoagulants.[14] If the bleeding risk is thought to be high, the administration of anticoagulants can be restarted at prophylactic LMWH doses and upgraded to intermediate or therapeutic doses as soon as adequate hemostasis has been obtained.

In women with acute proximal DVT or PE after the 37th week of gestation, the risk of symptomatic PE during labor is substantially increased. In these cases, a planned delivery may be beneficial either through the induction of labor or by elective caesarean section because this allows events to be timed and minimizes the duration of time spent without adequate anticoagulation. Women treated with LMWH may be switched to a continuous infusion of UFH at least 36 hours before the induction of labor or caesarean section. UFH has a shorter half-life and should be discontinued 4 to 6 hours before anticipated delivery. In cases supposed to have a markedly increased risk of PE, the infusion rate may be downregulated (e.g., 400–600 IE/h) to maintain anticoagulation as long as possible, and the infusion may be discontinued only for the ejection phase of delivery.[14,36] In the absence of bleeding complications, the infusion may be restarted 4 to 6 hours after delivery. A retrievable inferior vena cava (IVC) filter may also be considered to prevent PE during delivery. Given limited experience with these devices peripartum and in consideration of 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.[32,68,69]

Postpartum Anticoagulation

Despite the inconvenience of subcutaneous injections, many women prefer to stay on LMWH therapy postpartum because they are used to its administration and they do not have to undergo regular international normalized ratio (INR) monitoring while caring for the newborn.[70] Small amounts of LMWH have been detected in the breast milk. Because the bioavailability of orally administered heparins is negligible, traces of LMWH in the breast milk are considered harmless to the child.[71] Warfarin and acenocoumarol are polar, non-lipophilic, and highly protein-bound, so excretion in significant amounts into breast milk is unlikely.[6] Switching to these VKAs is an alternative option to on-going LMWH treatment but requires an overlapping period with LMWH of approximately 5 days with frequent INR monitoring to achieve an INR target range of generally 2.0 to 3.0.[6,32]

Table 3 Neuraxial anesthesia in patients treated with therapeutic doses of anticoagulants[13,65]

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 anesthesia should be avoided due to a long half-life and potential accumulation	
Danaparoid, therapeutic dose	24 h		

Abbr.: i.v., intravenous; LMWH, low-molecular-weight heparin; s.c., subcutaneous; UFH, unfractionated heparin.
Note: Minimum time intervals without anticoagulation before and after catheter placement and removal according to the recommendations of the German Society of Anaesthesiology and Intensive Care Medicine: 25% residual anticoagulant activity remains after 2 half-lives, providing attenuated protection against thrombosis and a reduced bleeding risk, which generally allows the use of neuraxial anesthesia. 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.

Therapeutic Options in Life-Threatening PE

Systemic thrombolysis must be regarded as contraindicated during pregnancy and in the peripartum period and should be reserved for life-threatening cases of PE, i.e., cases who are hemodynamically unstable.[5,6] Low-molecular weight fragments of urokinase cross the placenta. Recombinant tissue plasminogen activator (rt-PA) and streptokinase are larger molecules, but minimal transplacental passage has been demonstrated for these drugs. There are therefore concerns about severe adverse effects, such as bleeding complications, pregnancy loss, premature labor, and placental abruption.[72]

A recent review of the literature identified 127 cases of severe PE (23% experienced cardiac arrest) who were treated with either thrombolysis or surgery. Among 83 women with thrombolysis, survival was 94%. The risk of major bleeding was 18% during pregnancy and 58% in the postpartum period. Fetal death possibly related to PE or its treatment occurred in 12%.[73] If a pregnant woman with acute PE is hemodynamically unstable and not suitable for thrombolysis or if thrombolysis has failed, endovascular or surgical embolectomy must be considered.[72] The decision regarding which method should be applied depends on the local expertise and available resources.

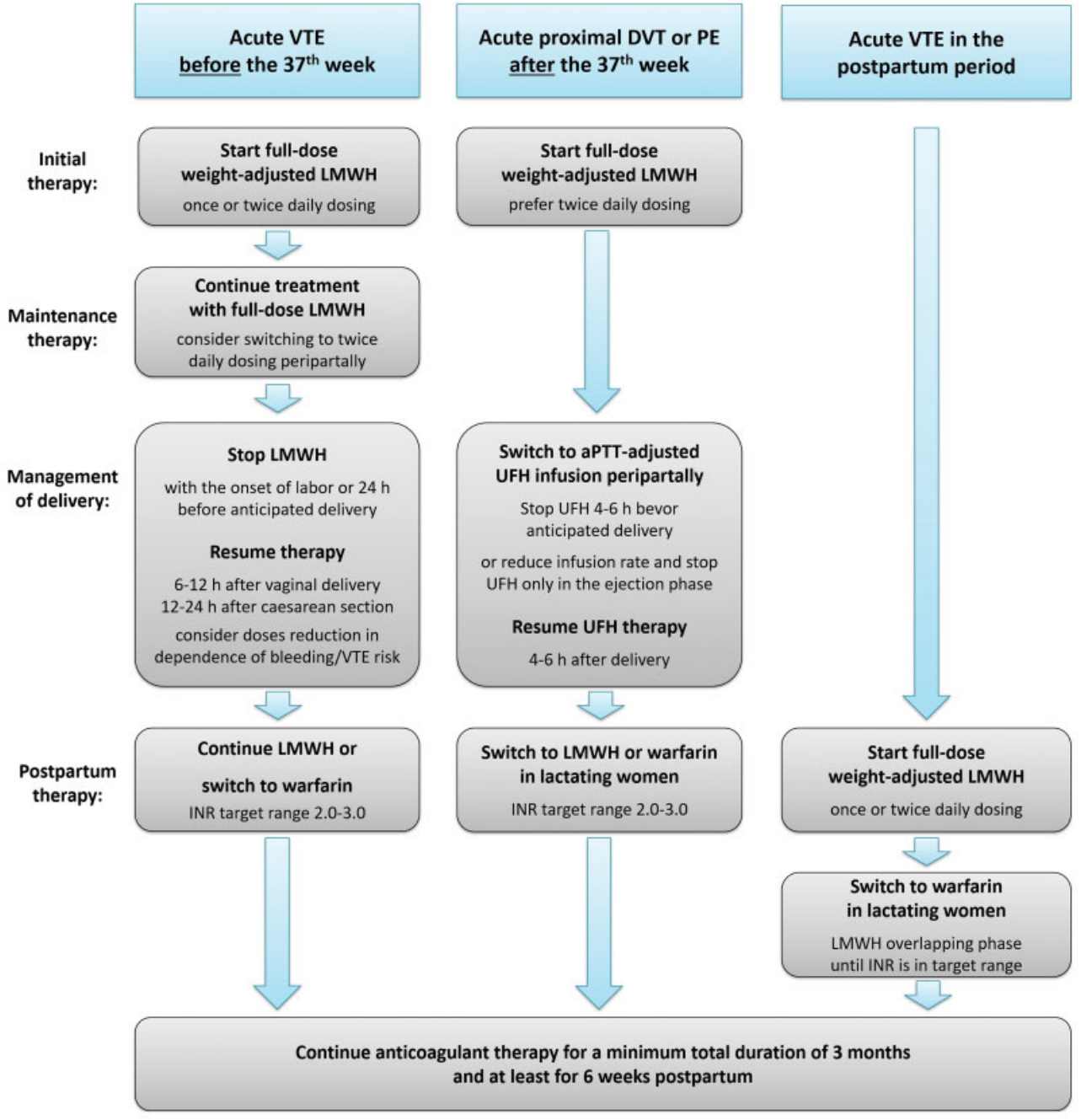

Fig. 1 Suggested approach for anticoagulation therapy of VTE during pregnancy and postpartum (adapted from Linnemann et al[14]). DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism; UFH, unfractionated heparin.

IVC filter insertion in pregnant women treated with anticoagulants is not recommended unless recurrent PE occurs despite adequate anticoagulation or when severe contraindications to anticoagulant therapy exist.[14,32,33] Temporary filter placement may also be considered in the peripartum period if acute iliofemoral DVT occurs after the 36th week of gestation. However, their use in pregnant women is limited to case reports or small case series, and it remains uncertain whether they are beneficial in this setting. Each case therefore requires individual assessment, and the risks of filter placement and complications (e.g., filter migration, fracture, perforation, radiation exposure) must be considered.

Long-Term Outcomes after Pregnancy-Related VTE

PTS. Because pregnancy-related DVT often involves the iliac and femoral veins, a substantial number of women are expected to develop long-term sequelae following extensive DVT. In a long-term follow-up over 3 to 16 years, women with pregnancy-related 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 (odds ratio [OR]: 6.3; 95% confidence interval [CI]: 2.0–19.8).[74]

VTE recurrence after pregnancy-related VTE. Compared with women with unprovoked VTE, women with pregnancy-related VTE have a significantly lower long-term risk of VTE recurrence than patients with unprovoked VTE (5.8 vs. 10.4% per year).[75] Of note, the risk of recurrent VTE is substantially increased during a subsequent pregnancy (absolute risk 2–10%; OR: 24.8; 95% CI: 17.1–36.0) compared with pregnant women without previous VTE.[76] The risk increase depends on the circumstances under which the first VTE occurred. These findings should be considered when decisions are made about VTE prophylaxis in women with a history of pregnancy-related VTE. For further risk assessment and recommendations for secondary prevention of VTE during pregnancy, we refer to a subsequently published position paper from the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH).[77]

Conclusions

There is a lack of adequate study data. Thus, management strategies for pregnancy-related VTE must be deduced from observational studies and extrapolated from studies performed in nonpregnant patients. Weight-adjusted, full-dose LMWH is the anticoagulant treatment of choice during pregnancy. Both once- and twice-daily LMWH dosing regimens are suitable. Using routine aXa measurement to monitor LMWH therapy during pregnancy cannot be recommended. It remains unclear whether the full-therapeutic LMWH dose can be reduced to an intermediate-dose regimen for secondary prevention of VTE during on-going pregnancy. According to current evidence, there is no support for the routine use of VKA, DOACs, fondaparinux, or danaparoid in uncomplicated pregnancy-related VTE. Pregnant women with VTE should be followed closely throughout pregnancy. The management strategy of anticoagulation at delivery deserves special care and attention and depends on the time interval between the diagnosis of acute VTE and the expected delivery date. If VTE manifests after the 37th week of gestation, the risk of PE at the time of delivery is generally high. The different anticoagulant management strategies currently in use during pregnancy and peripartally are summarized in ►**Fig. 1**. We conclude that there is an urgent need for well-designed prospective studies to compare different management strategies in women with VTE related to pregnancy and the postpartum period.

Conflicts of Interest

B.L. received honoraria and/or travel reimbursements over the last three years for lectures and consultancy work related to the topic of this article from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Siemens Healthcare. S.H. received honoraria and/or travel reimbursements over the last three years for lectures and consultancy work related to the topic of this article from Roche, Stago, CSL Behring, Daiichi Sankyo, and Swedish Orphan Biovitrum. C.H. received honoraria and/or travel reimbursements over the last three years for lectures and consultancy work related to the topic of this article from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Leo Pharma.

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