REVIEW ARTICLE

Venous thromboembolism in pregnancy: recent advances

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ABSTRACT

Venous thromboembolism (VTE) is notably more common in pregnancy, with at least a 5-fold higher risk than in nonpregnant women, and an even greater surge postpartum. Pregnancy induces a hypercoagulable state with venous stasis and vascular changes, making VTE a leading cause of maternal morbidity and mortality, particularly in the postpartum period. Clinical presentation is often subtle or nonspecific, highlighting the need for objective diagnostic strategies adapted to pregnancy. Emerging diagnostic algorithms, including D-dimer–guided approaches and pregnancy-specific rules, such as the pregnancy-adapted YEARS criteria, are improving diagnostic accuracy while limiting unnecessary imaging. Prevention and treatment regimens are tailored to pregnant patients, with low-molecular-weight heparin remaining the cornerstone of therapy. Ongoing research is exploring individualized prophylaxis based on personal risk profiles, biomarker-driven risk stratification, and optimized postpartum management protocols. Under-recognized issues, such as superficial vein thrombosis and rare but high-risk thrombophilias (eg, antithrombin deficiency) are also garnering attention for their contribution to pregnancy-associated VTE risk. This review provides a comprehensive update on pregnancy-related VTE, highlighting evolving concepts in epidemiology, diagnosis, prevention, and management of deep and superficial venous thromboses and pulmonary embolism from pregnancy through the postpartum period.

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Introduction Pregnancy is an independent risk factor for venous thromboembolism (VTE) and remains one of the leading nonobstetric causes of maternal mortality. The increased risk during pregnancy is multifactorial, with all 3 components of the Virchow triad—hypercoagulability, venous stasis, and endothelial injury present. Hormonal changes lead to increased venous capacity in the lower limbs and pelvis, resulting in reduced blood flow. This is exacerbated by estrogen effects and mechanical compression exerted by the enlarging uterus. Additionally, venous endothelial damage may occur during delivery. However, the most significant contributing factors are the pregnancy-induced alterations in coagulation and fibrinolysis.

Hemostatic changes during pregnancy and postpartum Pregnancy is characterized by a pronounced procoagulant state, probably an evolutionary adaptation aimed at minimizing hemorrhage during childbirth, therefore, VTE is a leading cause of maternal death in developed countries.[1,2]

Localized intravascular coagulation occurs particularly within the placental vessels. This leads to a physiological reduction in platelet count. Coagulation factors (Fs) such as FV, FVII, FVIII, FIX, FX, FXI, FXII, von Willebrand factor,

and fibrinogen are all elevated. Antithrombin and protein C levels show minimal change, but the protein C-dependent pathway becomes less efficient due to alterations in thrombomodulin and the protein C receptor levels—an effect termed acquired activated protein C resistance. This condition mimics the congenital form seen in individuals with FV Leiden mutation. Furthermore, protein S levels decrease during pregnancy, enhancing the prothrombotic state.

In contrast, fibrinolysis, a mechanism counter-regulatory to coagulation, is suppressed due to elevated levels of plasminogen activator inhibitors 1 and 2 (PAI-1, PAI-2). Consequently, D-dimer levels increase and continue to rise throughout gestation.[3]

The postpartum period—the first 6 weeks after delivery—marks a gradual return to the nonpregnant hemostatic state. This is completed by the 12th postpartum week.[4]

Epidemiology The risk of VTE, which includes mainly deep venous thrombosis (DVT) and pulmonary embolism (PE), is approximately 4 times higher during pregnancy than in nonpregnant women of the same age. Still, the absolute risk remains low, with an incidence of about 199 per 100 000 pregnant women/years.[5] A Swedish registry detected 49.3 cases of PE and 101.5 cases of DVT per 100 000 deliveries, and found a decreasing incidence of DVT and increasing incidence of PE in recent years.[6] The clinical implications are significant. Of VTE cases, approximately 20% manifest as PE and 80% as DVT, with an overall incidence between 0.06%–0.13%. While the incidence of DVT has been decreasing, likely due to better prophylactic practices, the PE rates have remained unchanged or are increasing.[1,2,6]

VTE is slightly more common in the third trimester than at earlier stages of pregnancy. Notably, nearly half of all VTE events occur postpartum, with the majority happening within the first 6 weeks, and very few after the 10th week postpartum.[7] PE continues to be the leading cause of maternal death in developed countries, responsible for 0.8 to 1.49 deaths per 100 000 pregnancies,[8,9] accounting for about 10% of all maternal deaths, with a case fatality rate of approximately 3%. PE is now more prevalent as a cause of maternal death than hemorrhage, preeclampsia, and sepsis combined.[8] Chronic complications of DVT, such as post-thrombotic syndrome, also pose significant functional and morphological problems.[10] It was found that interrupted pregnancies, besides lower-limb DVT and AB blood group, were risk factors for VTE recurrences.[11]

Risk factors VTE during pregnancy and the postpartum period arises from a complex interplay of multiple risk factors, encompassing both pre-existing medical conditions, pregnancy-specific physiological changes (TABLE 1), and concomitant diseases.[12-15]

Approximately 50% of pregnant women who develop VTE present with at least 1 identifiable risk factor.[11] Importantly, these conventional risk factors often confer a higher relative risk in the pregnant population, as compared with the general female population. Furthermore, several risk factors are unique to pregnancy and postpartum, contributing to a more intricate risk assessment. The presence of multiple concurrent risk factors further amplifies the overall VTE risk in an additive manner, but the importance of risk factors or their combinations is sometimes assessed differently by different societies or guidelines.[16]

Clinical presentation The clinical presentation of VTE during pregnancy closely resembles that in the nonpregnant population. However, the physiological adaptations of pregnancy often obscure or mimic VTE-related symptoms. For instance, lower limb swelling is a frequent, benign occurrence in normal pregnancy, and dyspnea is commonly reported among healthy pregnant individuals. This symptom overlap results in a low diagnostic yield—VTE is confirmed in only approximately 10% of pregnant women undergoing evaluation for suspected disease.[2]

Despite the low yield, a high index of clinical suspicion is essential, particularly in the presence of identifiable risk factors. Diagnostic strategies must accommodate the unique physiological changes in pregnancy, while accounting for the limitations of conventional diagnostic tools in this population.

Diagnosis of deep vein thrombosis in pregnancy **Clinical assesment** Although clinical decision rules (eg, Wells or Geneva scores) are well validated in nonpregnant populations for assessing pretest probability of VTE, these models do not include pregnancy-specific parameters, and are therefore not reliably applicable in the obstetric setting. Several pregnancy-adapted risk scores have been proposed; however, validation data remain limited.[17] Regardless, clinical assessment remains the first step in evaluation, followed by targeted objective testing.

D-dimer testing D-dimer, a fibrin degradation product, is commonly used to rule out VTE in nonpregnant individuals. However, its utility in pregnancy is limited by physiological increases in D-dimer concentrations, particularly in the second and third trimesters, which reduce test specificity and lead to an increased rate of false-positive results. Consequently, some guidelines advise against routine use of D-dimer testing during pregnancy.[12]

Nonetheless, recent evidence supports a selective use of D-dimer in the context of an integrated diagnostic algorithm tailored for pregnancy, particularly when the levels are below a validated threshold and clinical suspicion is low.[18] D-dimer testing is also used in algorithms for the diagnosis of PE during pregnancy.[19]

TABLE 1 Risk factors for venous thromboembolism in pregnancy and the postpartum period (adapted from[12-15])

Category	Risk factor	Relative risk[a]
Medical conditions	Obesity (BMI >30 kg/m^2)	5.3
	Strict bed rest ≥1 week	>6 (range, 7–62)
	Comorbidities (eg, heart disease, connective tissue disorders)	7–10
	Anemia	2
	Blood transfusion	7
	Previous VTE	25
	Smoking	2
	Diabetes mellitus	2
	Drug abuse	1.1
	Hypertension	1.8
	Antiphospholipid antibodies	16
	Family history of VTE	2–4
Pregnancy-related	Age >35 years	2
	Cesarean delivery – elective	2
	Cesarean delivery – urgent	4.6
	Multiparity	1.6
	Infection after vaginal delivery	20
	Infection after caesarean delivery	6
	Assisted reproduction	4.4
	Preeclampsia	3.8
	Eclampsia	4.4
	Placenta previa	3.6
Thrombophilias	FVL (heterozygous)	8.3
	FVL (homozygous)	34 (range, 10–40)
	Prothrombin gene mutation (heterozygous)	6.8
	Prothrombin gene mutation (homozygous)	26
	Combined FVL and prothrombin mutations	9–107
	Protein S deficiency[b]	8
	Protein C deficiency[b]	4.8
	Antithrombin deficiency[b]	4.7–10

a Relative risk >6 corresponds to an estimated about 3% absolute risk of VTE.

b Due to the rarity of these inherited disorders, risk estimates may be conservative.

Abbreviations: BMI, body mass index; FVL, factor V Leiden; VTE, venous thromboembolism

Ultrasound examination Compression ultrasound (CUS) is the imaging modality of choice for suspected DVT during pregnancy. It is noninvasive, widely available, and highly reliable, with sensitivity of 94% and a negative predictive value of 99%. Two principal strategies are utilized: 1) serial proximal CUS to examine the femoral and popliteal veins; if the initial scan is negative but clinical suspicion persists, repeat imaging after 7 days is advised; and 2) whole-leg CUS to assess the entire lower extremity venous system, including the calf veins. This approach may eliminate the need for follow-up imaging.

Whole-leg ultrasound is often favored at the initial presentation, particularly in the cases of moderate-to-high clinical suspicion. Repeat imaging is indicated if symptoms persist despite an initial negative scan.[13] CUS is also effective in evaluating suspected upper extremity DVT.

Standard ultrasound is less effective for detecting iliac vein thrombosis due to limited visualization of the pelvic veins. This limitation is clinically relevant, as isolated iliac or pelvic vein thrombosis is more common in pregnancy, particularly in the third trimester. It may manifest with unilateral leg swelling, back pain, or flank discomfort.

Because the iliac veins are not easily compressible, indirect findings—such as absent Doppler flow or visualized thrombus—may support the diagnosis. However, diagnostic accuracy remains limited. In the cases of high clinical suspicion with inconclusive ultrasound findings, magnetic resonance imaging without contrast or conventional phlebography should be considered.[20-22]

Pulmonary embolism in pregnancy The diagnosis of PE during pregnancy necessitates a systematic approach to minimize both maternal and fetal risks while ensuring diagnostic accuracy. Nowadays, there are 2 evaluated diagnostic strategies. The first one is based on the CT-PE study by Righini et al.[23] The initial evaluation should begin with a clinical assessment based on the pregnancy-adapted Geneva score (TABLE 2), followed by lower-limb CUS and D-dimer testing, and computed tomography pulmonary angiography (CTPA).

When CUS findings are positive for DVT, a diagnosis of PE is strongly suspected and treatment regimens for DVT and PE are usually the same.

In the cases where DVT is not detected on ultrasound, further diagnostic imaging is required. CTPA is commonly recommended due to its high sensitivity in detecting PE.[23,24] Although concerns related to radiation exposure are valid, the maternal risk is chiefly related to a slightly elevated breast cancer risk, and the fetal radiation dose remains minimal, especially with contemporary imaging technologies. A special pregnancy-adapted low-dose CTPA protocol is also described, which minimizes the risk of radiation due to the procedure.[25]

Alternatively, a diagnostic pathway may involve an initial chest X-ray. If normal, a subsequent ventilation-perfusion (V/Q) scan is indicated. It is noteworthy that while V/Q scanning tends to result in a lower radiation dose for the mother than CTPA, the fetal dose may be marginally higher; however, both remain within acceptable safety margins.[26] The principal challenge with both modalities lies in their diagnostic performance, particularly in the lung bases, where an elevated diaphragm may yield inconclusive results.

The second strategy for PE diagnosis follows the YEARS algorithm,[27] which uses the presence of clinical signs of DVT, hemoptysis, and the likelihood of PE as the primary criteria. They can obviate the need for CTPA in the cases where D-dimer levels are below 1000 ng/ml (in the absence of these criteria) or below 500 ng/ml (when 1 or

TABLE 2 Pregnancy-adapted Geneva risk score[a] (adapted from[23])

Variable	Points
Age 40 years or older	+1
Surgery (general anesthesia) or lower limb fracture in the past months	+2
Previous DVT or PE	+3
Unilateral lower limb pain	+3
Hemoptysis	+2
Pain on lower limb palpation and unilateral edema	+4
Heart rate >110 bpm	+5

a Pregnancy-adapted Geneva risk score interpretation:
0–1 points: low PTP; PE prevalence in the development cohort, 2.3%; 95% CI, 1–4.9
2–6 points: intermediate PTP; PE prevalence in the development cohort, 11.6%; 95% CI, 6.9–18.9
≥7 points: high PTP; PE prevalence in the development cohort, 61.5%; 95% CI, 35.5–82.2

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PTP, pretest clinical probability

more criteria are present). When clinical signs of DVT are present, CUS of the affected limb should also be performed. Previous data have indicated that only approximately 10% of pregnant women with suspected PE require CTPA.[26] Both regimens, that is, CT-PE and YEARS algorithm, were evaluated and could be used in PE diagnostics.[28] The choice depends on the preference of the center.

Superficial vein thrombosis Superficial vein thrombosis (SVT) is a neglected disease in pregnancy, although its prevalence is about 0.1%,[24] and the risk of concomitant VTE is about twice as high as in pregnant women without SVT.[29,30] In a nation-wide Danish study, SVT was diagnosed during the whole pregnancy and more commonly postpartum, when the incidence rate was 1.6 per 1000 person-years (95% CI, 1.4–1.7).[31] The clinical picture is more evident than in DVT. It consists of pain, tenderness, and inflammatory reactions along the course of the affected vein. However, ultrasound examination is still needed to assess the thrombosis extension. This is suggested especially when SVT affects the great or small saphenous veins.[30] SVT is an equivalent of DVT, when it extends 3 cm near the confluence of the superficial vein system into the deep one, and in that case, it should be treated as DVT.[32] The treatment in other cases is less clear. The American Society of Hematology (ASH) guidelines[24] suggested that SVT should be treated with low-molecular-weight heparin (LMWH) till the end of pregnancy and 6 weeks postpartum. However, the dosage is not mentioned.[24] A recent position paper suggests LMWH at a prophylactic dose for below-knee SVT for 6 weeks. If there are additional risk factors for VTE, the treatment is extended. For SVT above the knee, but at least 10 cm from the junction of the superficial and deep venous system, the treatment with an intermediate dose of LMWH is suggested, lasting for the whole pregnancy and 6 weeks postpartum. SVT extending closer than 5 cm to the junction to the deep venous system is equivalent of DVT, and it is treated the same as DVT. Compression stockings can also be used.[30]

Testing for different types of inherited thrombophilia is not necessary at diagnosis of SVT, as the results are not going to influence the therapeutic strategy regarding the initiation of the anticoagulant treatment or its intensity and duration throughout pregnancy. Testing for lupus anticoagulant (LA) and antibodies related to the antiphospholipid syndrome (APLS) might influence the decision regarding the dose of LMWH (ie, in the case of a positive test, administration of a therapeutic dose of LMWH could be considered) or the addition of aspirin. From this point of view, the Balkan Working Group proposes that the tests for LA and APLS-related antibodies are performed soon after the diagnosis of SVT.[30] However, this is debatable, as the test results, especially those for LA, a laboratory criterion for APLS, could be changed in the acute phase of a new VTE event.[33]

Although the CALISTO trial (Evaluation of Fondaparinux 2.5 mg Subcutaneously Once Daily for the Treatment of Superficial Thrombophlebitis) confirmed fondaparinux to be both effective and safe for treating SVT, it did not include pregnant women. Since small amounts of fondaparinux may cross the placental barrier and enter the fetal bloodstream, the trial's results cannot be directly applied to this population. Therefore, fondaparinux should not be regarded as the first-line antithrombotic option during pregnancy. As a result, its use is not recommended as an initial treatment for SVT in pregnant women.[30,32]

We can conclude that there are not enough studies describing SVT in pregnancy, and therefore we must rely on expert opinions.

In diagnostic workup, there is no need for thrombophilia testing in pregnancy with already diagnosed VTE,[19] but it could be informative for further assessment after pregnancy.

Antiphospholipid syndrome in pregnancy APLS is a systemic autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity, with laboratory evidence of persistent antiphospholipid antibodies. These antibodies include LA, immunoglobulin (Ig) G/IgM, anticardiolipin (aCL), and/or anti-β-2 glycoprotein I antibodies, which must be detectable on 2 occasions at least 3 months apart.[33] Obstetric APLS (OAPLS) is defined also by the presence of pregnancy complications that may include the following criteria: 1) 3 or more consecutive early fetal losses (<10 weeks of gestation); 2) at least 1 fetal demise occurring after 10 weeks of gestation; 3) premature delivery before 34 weeks due to severe conditions, such as preeclampsia or placental insufficiency leading to fetal growth restriction.[34]

It is important to recognize that the clinical criteria for OAPLS are relatively nonspecific. They overlap with other conditions that may

arise during pregnancy and are attributable to genetic, chromosomal, obstetric, or endocrine abnormalities.[35] Moreover, the interval between the detection of positive APLS-related antibodies and the occurrence of relevant clinical events should not exceed 3 years.[36]

For women with an established diagnosis of OAPLS, therapeutic management in subsequent pregnancies should include prophylactic administration of LMWH in combination with low-dose aspirin (100 mg/day). Following delivery, aspirin is typically discontinued, with LMWH being continued up to the 6th postpartum week.[35]

Treatment The treatment of VTE during pregnancy generally aligns with protocols used in nonpregnant populations, though certain pregnancy-specific considerations are essential.

Anticoagulant treatment Vitamin K antagonists are contraindicated during pregnancy due to their teratogenic effects and a risk of fetal bleeding. Although possibly acceptable very early in the first trimester (before the 6th week), their use is generally restricted to the postpartum period, where they are safe during breastfeeding. Direct oral anticoagulants—including rivaroxaban, dabigatran, apixaban, and edoxaban—are also contraindicated during both pregnancy and lactation.[26,37]

In contrast, unfractionated heparin (UFH) and LMWH do not cross the placenta and are safe for use during pregnancy. LMWH, in doses prescribed by a manufacturer (therapeutic ones) adjusted to the body weight, is preferred due to its more predictable pharmacokinetics and lower risk of complications. UFH may be utilized around the time of delivery or in procedures with a high risk of bleeding due to its shorter half-life and complete reversibility.

Bleeding complications associated with LMWH are uncommon, occurring in approximately 2% of cases: 0.4% before delivery, 1% postpartum, and 0.6% postoperatively. Other potential adverse effects include allergic reactions (1.8%) and heparin-induced thrombocytopenia (0.025%).[24] Bone mineral loss is rarely reported (<0.04%) and may reflect the underlying physiological bone changes in pregnancy.[12]

For patients with APLS and acute DVT, 100 mg of aspirin is typically added to LMWH therapy, with aspirin discontinued after the 36th week of gestation. In heparin-induced thrombocytopenia, which is very rare, fondaparinux or danaparoid as anticoagulants could be considered.[28]

Low-molecular-weight heparin regimen LMWH is administered subcutaneously either once or twice daily, adjusted to the body weight. While twice-daily dosing may be preferable due to increased renal clearance during pregnancy, once-daily dosing has also proven effective and remains a standard practice.[12,15,35] The twice-daily regimen is advisable during the final month of pregnancy, reverting to once daily postpartum.

For individuals weighing over 100 kg, manufacturers recommend a twice-daily dosing schedule, consistent with dosing in nonpregnant individuals.

The recommended duration of anticoagulation is throughout pregnancy and for 6 weeks postpartum. In the cases of late-onset DVT (eg, in the final weeks of pregnancy), treatment should extend for at least 3 months or even 6 months from the time of diagnosis.[12,24,26,28,37]

Monitoring of anticoagulation therapy Monitoring of LMWH via anti-Xa levels is generally not required during pregnancy, as current data do not support dose adjustments based on these levels.[24,26,37] However, in selected high-risk scenarios, anti-Xa monitoring may be warranted, for example for: 1) the twice-daily LMWH regimen, the target anti-Xa level (measured 4 h postdose) is 0.5–1 IU/m; 2) the once-daily dosing, a target range of 1–2 IU/ml (4–6 h postdose) is considered acceptable.

The use of anti-Xa testing in patients treated with therapeutic dosages of LMWH is recommended by only 2 guidelines,[15,38] and otherwise discouraged. Some authors propose to monitor patients with obesity or those with renal insufficiency.[39] Obesity is a VTE risk factor, but it is also a problem in the treatment of VTE in pregnancy, because the dosages could be high. In those patients, anti-Xa monitoring is justified, as it is more reliable than relying solely on body weight.

In some patients, when anti-Xa testing is used, and the result is lower than expected, antithrombin deficiency (ATD) could be considered, as the anticoagulant effect of LMWH is highly dependent on AT activity, and it may be reduced in women with ATD. In that case, an anti-Xa assay without exogenous AT is recommended to avoid overestimating the anticoagulant effect of LMWH in patients with ATD. With the twice-daily dosing regimen, a peak anti-Xa value of 0.5–1 IU/ml is expected.[15] There is no clear recommendation on what to do if the anti-Xa target level after adjustment is not reached and ATD is detected. One of possible strategies is to normalize AT levels by administering an AT concentrate together with LMWH treatment, but this strategy is based only on expert opinion and some reports.[40] The guidelines recommend the use of AT concentrate only at the onset of labor.[15] Due to insufficient data, the use of AT concentrate is highly individulized, but therapeutic dosages of LMWH should be continued. A recent study proposes AT concentrate substitution in pregnant women who develop recurrent VTE while on therapeutic LMWH, and also in the peripartum period.[41] Administration of 1 IU/kg of AT concentrate will increase circulating AT levels by around 2% in patients with inherited ATD. The dosage of AT concentrate could be calculated according to the formula:

(desired AT level% – baseline AT level%) × body weight [kg]/1.4 = units of AT required.[41]

TABLE 3 Dosing of low-molecular-weight heparins in prophylactic, once-daily dose (adapted from[51])

Body weight	Nadroparin, IU	Dalteparin, IU	Enoxaparin, IU	Tinzaparin, IU
<100 kg	2850	5000	4000	3500
>100 kg	3800	7500	6000	4500

UFH should be monitored using activated partial thromboplastin time, following standard practice; however, anti-Xa adjusted for UFH is a preferred option,[42] if it is available.

Management of acute venous thromboembolism near term In women approaching term, the decision to interrupt anticoagulation must carefully weigh the risk of recurrent VTE against bleeding complications. There are no universally accepted guidelines for this scenario, but the following approach is suggested: 1) administer LMWH in the twice-daily regimen during the final month; 2) administer the last half-dose on the day before delivery; 3) resume anticoagulation 12 hours postpartum.

For patients with recent VTE (<2 weeks before term), stopping anticoagulation without protection is discouraged due to a high risk of fatal recurrence. In such cases, the placement of a retrievable inferior vena cava (IVC) filter could be considered, especially if induction is planned.

In general, the first postpartum LMWH dose should be administered 6–24 hours after delivery, depending on the delivery method and bleeding risk. In the case of cesarean section, where bleeding risk is elevated, LMWH administration should still follow the same timeframe (6–12 hours postpartum).[12,13,26,28]

Neuraxial anesthesia and anticoagulation Special timing considerations are required for neuraxial anesthesia: 1) catheter placement should occur at least 24 hours after a half-therapeutic LMWH dose; 2) after catheter removal, LMWH should be resumed no sooner than after 2 hours (prophylactic dose) or 12 hours (half-therapeutic dose).[37,42]

Recanalization procedures for pulmonary embolism Pregnant patients with high-risk PE (eg, with hypotension or circulatory collapse) face a 37% case fatality rate.[9] In such scenarios, recanalization strategies, including thrombolysis or catheter-directed thrombolysis, catheter-directed thrombus aspiration, or extracorporeal membrane oxygenation should be considered. Surgical embolectomy remains another viable but rarely used option.[42]

Inferior vena cava filters The indications for IVC filter placement during pregnancy are consistent with those in the general population. The filters are considered in the case of acute VTE with contraindications to anticoagulation or recurrent VTE despite appropriate anticoagulant therapy.[43]

However, failure to retrieve the filter appears to be more likely to occur in pregnancy.[44,45]

Prophylaxis of venous thromboembolism in pregnancy Knowing several risk factors in women before pregnancy, it is logical to think about prophylaxis. However, there are different risk factors (TABLE 1) and different combinations of them, and therefore, prophylaxis is proposed differently by different societies.[26,46] A study that included 21 019 sequential postpartum VTE risk assessments found that in 19% of women, the risks appeared in the peri- or postpartum period and had not been present before.[47] It is obvious that risk assessment is needed before pregnancy, during it, and also postpartum, because besides basic risk some new risks can appear.[15]

The ASH guidelines propose prophylaxis when the risk of new pregnancy-associated VTE is 2% or higher.[24] Prophylaxis is sometimes also prescribed when the risk is lower according to different risk assessments, and it should be based on the patient's unique clinical risk factors.[39] In the Cochrane review, the need for prophylaxis in the women at risk was not estimated as evidence-based.[48] Consequently, the data about prophylaxis are sometimes inconclusive and guideline recommendations are mainly based on expert opinion rather than high-quality evidence.[49]

Prophylaxis could last for the whole pregnancy and postpartum or postpartum only. When in vitro fertilization procedures begin, prophylaxis can be also prescribed even before pregnancy is confirmed.

LMWH is typically used for prophylaxis at prophylactic dosage.[50] So-called low-dose LMWH (TABLE 3) has been confirmed as appropriate in the Highlow study, even in women with increased body weight.[51] In selected cases, probably very rarely, especially when women decline injections, warfarin for prophylaxis could be prescribed after delivery.[52] In a recent placebo-controlled study, aspirin (low-dose in Europe, 80 mg/day) has been used effectively to prevent postpartum VTE in women with several prepartum risk factors, such as mild-to-moderate inherited thrombophilia, antepartum immobilization, prepregnancy body mass index of 30 kg/m^2 or higher, prepregnancy smoking, previous SVT, and other pregnancy-related conditions.[53] The advantage of aspirin is that it does not need injections like LMWH, and it does not need controls like warfarin.

Women with a history of VTE during pregnancy or postpartum or while on hormonal treatment (including combined oral contraceptives) should receive prophylactic treatment in all future pregnancies, from the start until 6 weeks postpartum. The same applies to women with a prior unprovoked VTE (ie, without identifiable risk factors).[15,52,53]

In contrast, women whose previous VTE was triggered by a transient, nonhormonal risk factor do not require prophylaxis in future pregnancies, but they need prophylaxis after delivery.[24]

Patients with OAPLS should receive LMWH plus 100 mg of aspirin daily. For those with

thrombotic APLS, therapeutic doses of LMWH combined with aspirin are recommended.[34]

Common individual risk factors—such as obesity, advanced maternal age, multiparity, and smoking—do not warrant prophylaxis on their own.[24,39] However, when multiple risk factors are present, prophylaxis may be indicated.[15,24,52,53] A risk prediction model developed in the United Kingdom and evaluated in Sweden can help assess the combined risk. The model shows good correlation with actual outcomes (C statistic, 0.7; 95% CI, 0.67–0.73).[54]

Evidence on thrombophilia and the need for prophylaxis is mixed. Women with common thrombophilias, such as heterozygous FV Leiden or prothrombin mutation generally do not need prophylaxis. However, women with homozygous forms or multiple thrombophilic mutations need prophylaxis.[15,24,26,52] The same applies to women with protein C or S deficiency, when postpartum prophylaxis should be considered. In ATD, prophylaxis is recommended throughout pregnancy and the postpartum period.[39,46] According to the ASH guidelines, postpartum prophylaxis is recommended for women with certain thrombophilias (protein S deficiency, protein C deficiency, and ATD) and a family history of VTE in close relatives, whereas it is not indicated in the absence of a family history of VTE.[24]

Prophylactic anticoagulation in women with a low risk after caesarean delivery (but without additional risk factors) is also not a definitively resolved issue and is not uniformly treated. Some guidelines propose prophylaxis usually for 10 days, but if some other risk factors are present, prophylaxis can be prolonged to 6 weeks.[15] Some authors propose mechanical prophylaxis (mechanical pumps or compression stockings) only until ambulation, to decrease the risk of maternal mortality related to VTE,[55] but its inconvenience should be weighed against the bleeding risk.[52]

Prophylactic treatment is not without risk, usuallly of bleeding. It is rare, but estimated risks of major bleeding with prophylactic LMWH exsist (antepartum, 0%; 95% CI, 0%–0.6% and postpartum, 0.3%; 95% CI, 0%–1%).[26] It is also influenced by the time relation between the last prophylactic dose and delivery. However, there is no need for scheduled (induced) delivery.[24]

Future perspectives Several ongoing clinical trials are poised to address major gaps in the evidence regarding the prevention, diagnosis, and management of pregnancy-related VTE. For example, the LEaD study (Safely Ruling out Deep Vein Thrombosis in Pregnancy with the LEFt Clinical Decision Rule and D-Dimer; NCT02507180) is a prospective multicenter trial evaluating a diagnostic algorithm to rule out DVT in pregnancy, which combines the LEFt clinical decision rule with D-dimer testing.[56] Similarly, the PRESCOT study (Pregnancy and Risk of Venous Thromboembolism; NCT03659708) is investigating whether a personalized antepartum anticoagulation approach guided by the Lyon VTE risk score can safely reduce the incidence of VTE as compared with standard care.[57]

Beyond these, other trials are exploring innovative approaches to VTE prophylaxis and management in pregnant and postpartum women. For instance, the TROPHE study (Thrombinography in Pregnant Woman and in Vitro Action of Low Molecular Weight Heparin; NCT06575309) is assessing thrombin generation in pregnant vs postpartum women under in vitro exposure to LMWH to optimize dosing strategies.[58] Another notable trial is LACT (Excretion of Rivaroxaban in Human Breast Milk; NCT06831474), a phase I trial measuring rivaroxaban levels in breast milk of patients receiving prophylactic and therapeutic doses, with the goal of guiding postpartum anticoagulation choices for breastfeeding patients.[59] Additionally, the PREP and GO study (Prospective Evaluation of Peripartum Anticoagulation Management for Thromboembolism; NCT05756244) is an international cohort study examining peripartum anticoagulation management strategies (specifically, the timing of heparin interruption and resumption around delivery) and their impact on maternal outcomes, such as bleeding and recurrent VTE.[60] Moreover, an observational study (Effect of Low Molecular Heparin on Pregnancy Outcome With Protein S Deficiency; NCT06531525) is planned to monitor maternal and fetal outcomes as well as coagulation parameters in pregnant women receiving LMWH (enoxaparin) or aspirin, to better understand the broader impacts of these commonly used preventive therapies.

Taken together, these trials and related research initiatives aim to refine diagnostic algorithms, optimize prophylaxis (including dose and duration adjustments), and expand safe treatment options for pregnancy-related VTE. This collective body of work reflects a shift toward a personalized, evidence-based approach to VTE management in pregnant and postpartum women—one that balances efficacy with maternal and fetal safety.

Conclusions VTE is more prevalent in pregnancy than in age-matched nonpregnant women, primarily due to hormonal influences on coagulation, fibrinolysis, venous stasis, and vessel wall changes. Clinical manifestations can be nonspecific, necessitating an objective diagnostic workup. Diagnostic pathways mirror those in nonpregnant populations but should be adapted to account for physiological and anatomical changes in pregnancy.

Heparins, particularly LMWH, form the cornerstone of the treatment, as oral agents are contraindicated. Treatment of VTE during pregnancy, around the delivery, and postpartum is described. Anticoagulation should be continued for the duration of pregnancy and at least 6 weeks postpartum. Some patients need only prophylactic treatment, usually with low-dose LMWH

during pregnancy and 6 weeks postpartum, and some need prophylaxis only postpartum. There are a lot of indications for prophylaxis, but there are also differences in existing guideline recommendations, because the evidence for prophylaxis is weak. VTE treatment and prophylaxis during pregnancy pose a challenge, and due to its complexity, a multidisciplinary team should be involved.

ARTICLE INFORMATION

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