Risk factors, diagnosis and management of venous thromboembolic disease in pregnancy

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Venous thromboembolism in pregnancy is a leading cause of maternal morbidity and mortality. However, individualised clinical risk assessment and recent advances in clinical prediction rules for pulmonary embolism have the potential to improve management. https://bit.ly/3mjtHg2

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Abstract

Venous thromboembolism (VTE) in pregnancy is a leading cause of maternal morbidity and mortality. However, despite the significant associated clinical burden and potentially devastating societal impact, there is still a paucity of data surrounding its prevention and management. Consequently, international guideline recommendations vary widely. Exclusion of pregnant women from clinical trials in the past has contributed to knowledge gaps. However, recently published and ongoing studies demonstrate that excellent clinical trials in pregnancy are achievable. This review will discuss prevention, diagnosis and treatment of VTE in pregnancy, and will also explore priorities for future research.

Educational aims

- To gain an understanding of current knowledge on risk factors for pregnancy-associated venous thromboembolism (PA-VTE).
- To gain an understanding of the diagnosis of PA-VTE.
- To review up-to-date approaches to preventing and treating PA-VTE.
- To discuss possible limitations in current research and areas which require improvement.

Background

Venous thromboembolism (VTE) complicates approximately 1.2 of every 1000 pregnancies [1]. Thrombosis and thromboembolism are a leading cause of maternal morbidity in high-income countries [1, 2]. VTE (which includes deep venous thrombosis (DVT) and pulmonary embolism (PE)) remains the leading cause of direct maternal death during or up to 6 weeks after the end of pregnancy in the UK and Ireland [3]. Moreover, women who survive may have long-term health complications, including post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

The risk of pregnancy-associated VTE (PA-VTE) is elevated compared to the non-pregnant state in all three trimesters; however, it is reported to be greatest in the third trimester [2]. A systematic review and meta-analysis including 20 studies reported that the absolute incidence of VTE is equal during the antepartum and postpartum periods, at 0.6 per 1000 pregnant women [4]. However, given that the postpartum period is shorter than the antepartum period, the daily risk of VTE is greater in the postpartum period, with the greatest risk being evident in the first 6 weeks after delivery [5]. Women who develop a PA-VTE are at substantial risk of developing PTS, a potentially debilitating long-term complication, which is associated with a reduced quality of life [6]. The impact of VTE is far reaching, with the possibility of a potentially devastating fatal event, as well as (beyond the individual) bearing significant implications for the psychological wellbeing of the extended family, and for society.

In the UK and Ireland, while there has been a recognised decrease in the incidence of maternal mortality due to VTE, it is still suggested that more than two thirds of women's deaths assosciated with VTE could be prevented with improvements to care [3]. This review will discuss the current literature on PA-VTE, as well as emerging guidelines and information that may improve maternal care for this disease.

Risk factors

Pregnancy is a risk factor for the development of VTE, even in women with no additional risk factors [7]. The risk of VTE during the antenatal period is reported to be approximately four- to six-fold greater than in the non-pregnant patient and is reported to reach an up to 60-fold increase during the postpartum period [5, 8].

This pregnancy-associated elevated VTE risk can be attributed to the increased hypercoagulable state of pregnancy, a phenomenon that has been postulated to have evolved to prevent women from significant haemorrhage during childbirth and miscarriage [8]. The pathogenesis of this prothrombotic state can be explained by remembering the components of "Virchow's triad": 1) venous stasis, 2) endothelial damage, and 3) hypercoagulability. Venous stasis occurs as a result of a hormonally induced decrease in vascular tone and obstruction of venous flow by the enlarging uterus; this is most marked at 25–29 weeks gestation, when an approximately 50% reduction in venous flow may be observed, persisting until 6 weeks postpartum [9]. Endothelial damage can occur in the pelvic veins during delivery or as a consequence of venous hypertension [10]. Under physiological conditions, endothelial release of nitric oxide in the placental circulation dilates the fetal placental vascular bed, ensuring feto-maternal exchange. When local damage occurs, this results in disturbed production of angiogenic and anti-angiogenic factors, leading to systemic inflammation, endothelial activation, systemic oxidative stress and altered endothelial nitric oxide production [11]. The hypercoagulable state of pregnancy is also a major mechanistic contributor to thrombosis in pregnancy and includes an increase in fibrin generation, reduced fibrinolytic activity, an increase in coagulation factors II, VII, VIII and X, reduced protein S levels, and resistance to activated protein C [10].

Certain single risk factors are associated with a particularly high risk for development of a PA-VTE, including a "strong" hereditary thrombophilia (such as antithrombin deficiency with a strong family history), acquired thrombophilia, or a previous VTE event [9]. These factors are suggested to confer an absolute VTE risk of >1% [12].

Women with inherited thrombophilias have a higher risk of antepartum VTE than that reported for the general population (~0.6 of every 1000 deliveries) [2]. The magnitude of this risk increases depending on the specific thrombophilia, and the presence or absence of a family history of VTE [2]. Unfortunately, there is an inconsistency amongst national and international guidelines on optimal VTE prevention strategies for these women, due to varying estimates of thrombosis risk. For some, especially antithrombin deficiency, there are concerns that some studies overestimate this risk due to methodological limitations (referral bias and objective diagnosis). In a recent retrospective case–control study including 243 consecutive women with a history of first VTE during pregnancy or the puerperium and age-matched controls [13], women who were homozygous for the factor V Leiden (FVL) polymorphism, those who were compound heterozygous for FVL and prothrombin promoter region polymorphism G20210A, and those with antithrombin deficiency had a particularly high risk for pregnancy-associated thrombosis, especially if aged $\geqslant$35 years. This risk was similar to or higher than the risk that would result in consideration of prophylactic anticoagulation in the non-pregnant populations [13]. Compound heterozygosity for the FVL and prothrombin promoter region mutations appeared to be associated with a higher increase in risk than would be predicted by an additive risk [13].

While acquired thrombophilias have been less widely studied, it is suggested that persistent antiphospholipid antibody (APLA) positivity is associated with an increased VTE risk [9]. Heterogeneity in study design and included populations is likely to be responsible for the widely varying reported VTE rates in patients with APLA positivity.

Women with a personal VTE history have a high recurrence risk during pregnancy. Women at highest risk are those with a history of unprovoked or hormone-provoked VTE [14]. In a recent pooled analysis of four cohort studies, antenatal VTE recurrence rates during pregnancy without prophylaxis were reported to be 1.1% (95% CI 0.2–5.8%), 6.4% (95% CI 3.9–10.4%), and 3.6% (95% CI 1.4–8.9%) for provoked (non-hormonal), oestrogen-related, and unprovoked VTE, respectively [14]. VTE risk is further increased by additional risk factors (table 1 [12]), including maternal age >35 years, obesity, immobility, nulliparity, multiple gestations, smoking, hypertension, and recent surgery (caesarean section) [9].

TABLE 1 Risk factors for venous thromboembolism (VTE) during pregnancy and the postpartum period

Maternal characteristics		Pregnancy characteristics		Delivery characteristics	
Risk factor	**aOR**	**Risk factor**	**aOR**	**Risk factor**	**aOR**
Age >35 years	1.3	IUGR	3.8	Pre-term delivery	2.42.7
Parity ⩾3	2.4	Pre-eclampsia	2.9–3.1	Prolonged labour	NA
BMI ⩾25 kg·m^{-2}	1.8–2.4	Multiple gestation	1.7–4.2	Instrumental delivery	NA
Smoker	2.1–3.4			Caesarean section	1.8–3.6
Comorbidity	1.6–8.7			Stillbirth	6.4[#]
Varicose veins	2.4			MROP	2.2
Thrombophilia	3.2–34.4			PPH ⩾1000 mL	4.1
Prior VTE	24.8			Infection	4.1–6.1
Family history of VTE	NA			Immobility	7.7–10.8

Adjusted odds ratio (aOR) values are representative and, for clarity, confidence intervals are not included. BMI: body mass index; IUGR: intrauterine growth restriction; MROP: manual removal of placenta; PPH: postpartum haemorrhage; NA: not available. [#]: incident rate ratio. Reproduced and modified from [12] with permission.

VTE risk is dynamic and can change during pregnancy and postpartum if risk factors change. However, the interaction of VTE risk factors in determining absolute VTE risk remains a significant knowledge gap [15]. In a large hospital-based case–control study, VTE risk factors were validated by review of medical records. 559 women with objectively verified VTE during pregnancy or the postpartum and 1229 controls were included. The results of this study demonstrated that some risk factors had an additive effect (such as the combination of assisted reproductive technology with multiple pregnancy, and emergency caesarean section with infection), whereas other risk factors acted as multipliers (including the combination of antepartum immobilisation and elevated body mass index) [15].

In a recent cross-sectional study analysing the prevalence and patterns of VTE risk in over 21 000 sampled postpartum women in the population, 75% of women had at least one risk factor for VTE, and more than 40% carried at least two risk factors [16]. Given that the risk of VTE may increase in the presence of multiple risk factors, this high prevalence suggests a significant burden of VTE risk at a population level, even in the absence of well defined "high-risk" characteristics [17], and highlights the importance of VTE risk assessment in early pregnancy, in the postpartum period, and if risk factors change.

Prevention

Pharmacological thromboprophylaxis

Although the risk of VTE in pregnancy is increased 10-fold from baseline, the absolute risk of VTE in pregnancy remains low (0.6 per 1000 pregnancies) and, thus, most women do not require anticoagulation [18]. Low molecular weight heparin (LMWH) is the pharmacological agent of choice for antenatal and postnatal thromboprophylaxis and is administered parenterally *via* subcutaneous injection [19]. For women whose risk warrants pharmacological thromboprophylaxis, there remains no consensus on what the optimal dose should be, and guidelines have recommended regimens including a low prophylactic, intermediate and weight-adjusted dose of LMWH [9]. However, in most cases, the risks of anticoagulation outweigh the benefits [9]. The pitfalls of thromboprophylaxis during pregnancy include cost, inconvenient and painful administration, risk of bleeding, osteoporosis and heparin-induced thrombocytopenia (HIT). The International Society on Thrombosis and Haemostasis (ISTH) developed a single standardised definition of bleeding for use in non-surgical studies: a fall in haemoglobin of 2 g·dL^{-1}, or transfusion, or leading to a transfusion of ⩾2 units [20]. However, the pitfall is that international definitions of bleeding events are not well suited to pregnancy and the postpartum period. Therefore, the ISTH now proposes an adaptation of the definition of clinically relevant non-major bleeding to the context of pregnancy and postpartum, including the potential downgrading of certain events such as normal blood loss during delivery and first trimester bleeding to the category of minor bleeding or even non-bleeding events [21].

Although these complications are less common with LMWH than with unfractionated heparin (UFH) [9], the risks and benefits of pharmacological thromboprophylaxis should be individualised. Risk stratification is therefore required to determine which women should be considered candidates for pharmacological thromboprophylaxis. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends a formal VTE risk assessment for all pregnant and postpartum women [19]. These guidelines include an option to utilise a numerical risk assessment. Schoenbeck *et al.* [22] reported a significant increase in the proportion of patients who are risk assessed, earlier treatment, and greater consistency in clinical

decision-making when a numerical "scoring" system (risk assessment) is used, compared to a non-numerical system. Given that risk factors may be potentially reversible and can develop or resolve at later stages in gestation than the initial risk assessment, ongoing individual risk assessment is very important [19]. Each individual risk factor may confer a different absolute risk of VTE [18]. A large case–control study, conducted by Jacobsen *et al*. [23], including 613 232 births and 559 cases of antepartum and postpartum VTE (with an overall VTE incidence of 1 per 1000 live births) suggested that most previously identified pregnancy-related risk factors in isolation did not increase the absolute risk of antepartum VTE above 1%. This has recently been supported by a large population-based UK cohort study, investigated by Sultan *et al*. [24], which reported that, for example, the absolute risk of VTE associated with maternal obesity alone would not elevate predicted VTE risk sufficiently to warrant the use of thromboprophylaxis.

Several international organisations have published recommendations to guide the prevention of PA-VTE in clinical practice. However, while there is some (varying quality) evidence to guide the prevention of VTE in women at highest predicted risk (such as those with a prior VTE history), there is a scarcity of high-quality data to guide optimal prevention of PA-VTE in women with other recognised risk factors (figure 1 [14]). This has resulted in a lack of agreement amongst international guidelines, and thus in a striking variation in recommendations. These variations include the risk factors included in the risk assessment, the contribution of each risk factor towards the overall VTE risk and the risk threshold, dose and optimal duration of pharmacological thromboprophylaxis [17]. This has resulted in varying use of thromboprophylaxis, especially amongst postpartum women. Recently, a five-fold difference was reported in the number of women who would theoretically receive a recommendation of postpartum thromboprophylaxis, ranging from 7% under American College of Obstetricians and Gynecologists (ACOG) recommendations to 37% under those of RCOG [16]. This highlights the need for a high-quality, large-scale, prospective research study to determine best practices for effective prevention of PA-VTE [17]. Recent advances in score-driven risk prophylactic strategies include the STRATHEGE score. This was developed by 19 French experts in both the clinical management and research of PA-VTE, using a Delphi method. This score predicts a patient-specific estimation of risk during pregnancy and the puerperium and suggests prophylactic strategies accordingly. This tool has since been prospectively validated in a multicentre study among French maternity hospitals, involving over 2000 women at risk of either a VTE or placental vascular complications (PVC). This study comprised the outcomes of patients before and after implementation of the scoring system, and found that use of the STRATHEGE score and prophylactic strategies reduced VTE and PVC by 50% and 30%, respectively, without any significant increase in bleeding risk [25].

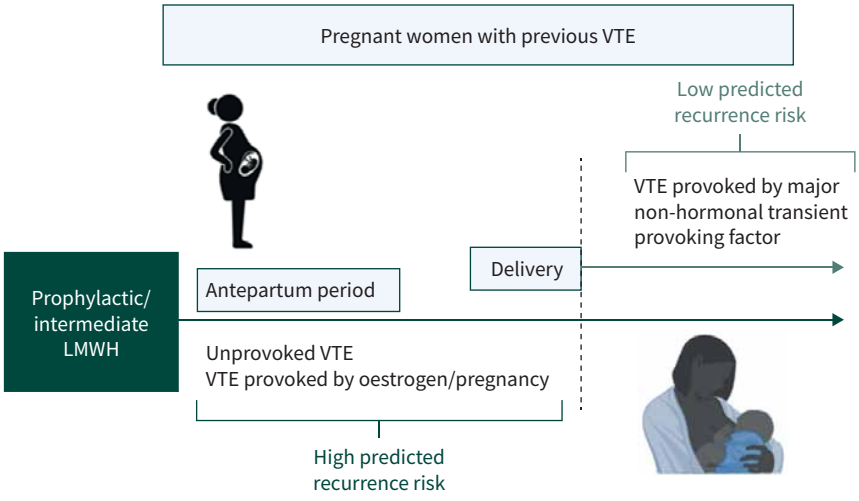

FIGURE 1 Venous thromboembolism (VTE) duration of anticoagulation based on risk. For pregnant women with prior VTE (especially those with an unprovoked or a hormone-provoked VTE), predicted recurrence risk during pregnancy is high enough to warrant both antenatal and postnatal thromboprophylaxis, whereas only postpartum thromboprophylaxis is recommended for women with lower predicted recurrence risks. The optimal low molecular weight heparin (LMWH) dose for women with prior VTE is currently being investigated in the ongoing Highlow study. Reproduced and modified from [14] with permission.

Mechanical thromboprophylaxis

Mechanical methods of thromboprophylaxis include graded compression stockings and intermittent pneumatic compression devices. Evidence for the use of mechanical thromboprophylaxis is extrapolated from non-pregnant surgical populations [18]. However, in the context of PA-VTE, available evidence is limited to observational studies [17]. Intermittent pneumatic compression devices in general surgery trials are associated with fewer major bleeding events when compared to heparin; however, they are associated with lower VTE risk reduction. Current recommendations suggest that when pharmacological thromboprophylaxis is not feasible (such as in the setting of active bleeding, thrombocytopenia, heparin allergy, or HIT), mechanical thrombophylaxis may be considered as an alternative. In women with a very high risk of VTE postpartum, mechanical thromboprophylaxis may be suggested as an adjunct to pharmacological thromboprophylaxis [18].

Diagnosis of VTE during pregnancy

The diagnosis of VTE during pregnancy can be challenging, as many clinical symptoms of DVT and PE may be mimicked by the swelling, discomfort and shortness of breath that accompanies normal pregnancy [9]. Moreover, diagnostic imaging may require exposure to ionising radiation [26]. Until recently, clinical prediction rules and D-dimer levels were not validated for use in pregnant patients [27]. However, with recent advances in clinical prediction rules for PE (although not yet for DVT), these strategies do now have the potential to improve management and avoid unnecessary radiological diagnostic tests.

Diagnosis of DVT during pregnancy

In pregnancy, compression ultrasonography (CUS) is recommended when DVT is suspected, as it is without risk, inexpensive and readily available [9]. A recent systematic review and meta-analysis reported sensitivity and specificity of 90.1% and 98.5%, 94.0% and 97.3%, and 97.9% and 99.8% for proximal leg, whole-leg, and serial CUS, respectively, in the diagnosis of DVT during pregnancy [28]. Recently published international guidelines recommend that lower limb CUS be performed for suspected DVT in pregnancy and should in some cases include imaging of the iliac veins and/or serial imaging if the initial CUS is negative [17]. CUS may be insufficiently sensitive for diagnosis of pelvic vein thrombosis. Contributing factors include their location and the fact that the increasing size of the uterus throughout pregnancy makes imaging of these veins in the latter half of pregnancy even more difficult [9]. Therefore, if CUS is negative, yet clinical suspicion remains high, magnetic resonance venography is suggested by international guidelines [26]. Magnetic resonance imaging also appears to be sensitive for isolated iliac DVT, which is more common in pregnancy [26]. Isolated iliac vein thrombosis may present with abdominal pain, buttock pain, back pain and/or swelling of the entire leg and therefore these symptoms should prompt specific iliac vein imaging. The left lower extremity is the most common site of DVT (~80%) in the pregnant and postpartum population. Contributing factors to this left-sided preponderance include compression of the left iliac vein by the left iliac artery, which is exacerbated by the enlarging uterus [9].

Diagnostic algorithms for suspected DVT in pregnancy

In past decades, diagnostic algorithms combining clinical symptoms, laboratory tests and imaging studies have been validated for the diagnosis of DVT and PE in the non-pregnant population and have excluded pregnant women [29]. Therefore, the derivation and validation of a diagnostic algorithm for DVT in pregnancy has been an important research priority [30]. The LEFt clinical prediction rule was recently derived to progress exclusion of DVT during pregnancy without the need for diagnostic imaging [31]. This model includes three variables (each assigned one point): symptoms in the left leg (L), calf circumference difference $\geqslant$2 cm (E), and first trimester presentation (Ft). According to this algorithm, pregnant women with 0 or 1 points are deemed to have an "unlikely" clinical probability, and those with >1 points a "likely" clinical probability [31]. In a retrospective cohort study including 157 pregnant patients (aiming to externally validate the LEFt rule), a DVT was diagnosed in 13 out of 111 (11.7%, 95% CI 8.3–20.9%) pregnant women with at least one of the LEFt criteria. No DVT was found in all 46 women who had no LEFt criteria (0.0%, 95% CI 0.0–7.9%). Limitations of this study included its retrospective nature and imprecision. Consequently, the LEFt rule is not yet ready for clinical use in ruling out DVT during pregnancy [30]. The ongoing prospective LEaD study (Safely ruling out deep vein thrombosis in pregnancy with the LEFt clinical decision rule and D-dimer: a prospective cohort study; ClinicalTrials.gov identifier NCT02507180) aims to evaluate the performance of the LEFt rule in an adequately powered prospective clinical management study. The primary outcome is the VTE rate at 90 days.

Diagnosis of PE in pregnancy

The potential radiation exposure risk of mother and fetus is an area of hesitancy when investigating suspected PE in pregnancy. However, this risk should be discussed with women, providing them with data on the competing risks of radiation exposure (which are extremely low, even when computed tomography

pulmonary angiography (CTPA) is performed, provided that "modern" low-radiation-dose protocols are used) and the consequences of missing a potentially life-threatening diagnosis [26]. It is crucial to establish a definitive diagnosis or to exclude PE when an event is clinically suspected. This is important due to the implications for ongoing care, such as prolonged anticoagulation therapy, delivery planning, potential prophylaxis in future pregnancies, and concerns regarding future use of oral contraception and oestrogen therapy [32]. However, this task can be very difficult to accomplish given that the clinical symptom of dyspnoea during pregnancy is physiological and multifactorial. Therefore, this poses the risk of over-suspicion of PE, and thus of subsequent radiation exposure, but also poses the crucial risk of under-suspicion, given that a number of diagnoses could be the culprit.

It is important to consider the welfare of the fetus and mother when making decisions about imaging [33]. Radiation doses of 100 mGy are associated with a combined increased risk of organ malformation and the development of childhood cancer; doses of <50 mGy are not associated with an increased risk of harm to the fetus. Radiation exposure associated with chest radiography, lung scintigraphy and CTPA exposes the fetus to <0.01 mGy, ~0.1–0.6 mGy and 0.05–0.5 mGy, respectively, which is well below the "harm" threshold of 50 mGy [32, 34]. CTPA and perfusion scanning appear to have similar negative predictive values and "false negative" rates when used to investigate women with suspected PE. In the past, CTPA was reported to deliver a radiation dose of as high as 20 mGy per breast. This exceeded the American College of Radiology recommendation of 3 mGy or less for standard two-view mammography. In contrast, perfusion scintigraphy delivers 0.11–0.31 mGy [33]. However, modern advances in computed tomography technology have significantly reduced the amount of radiation delivered to breast tissue, while also maintaining appropriate image quality. These methods include: 1) reducing anatomical coverage of the scan, 2) using iterative reconstructive techniques, 3) reducing the kilovoltage, and 4) reducing the contrast-monitoring component of the CTPA. Therefore, using modern imaging techniques, CTPA may expose the maternal breast to median doses as low as 3–4 mGy [34].

In a single-centre retrospective study, 99 pregnant women were exposed to a reduced peak kilovoltage monitoring scan of 80 kV and were compared with 84 pregnant patients using the conventional 120 kV contrast-monitoring protocol. The breast dose associated with the contrast-monitoring component alone was reduced by 88% in this pregnant population (0.25±0.67 *versus* 2.24±1.61 mGy; p<0.001). Overall, there was a 52% reduction in the CTPA-associated breast radiation dose (from 7.64 to 3.65 mGy) when using the protocol associated with a reduced kilovoltage. This radiation dose is significantly less than typically quoted doses in older literature, which may range from 10 to 70 mGy [35]. Modern CTPA techniques are associated with a negligible maternal cancer risk. Consequently, the avoidance of CTPA on the grounds of maternal cancer risk is no longer justified [34]. These findings are particularly encouraging as the clinical availability of CTPA along with ongoing radiation dose improvements has led to many departments using CTPA as their first-line diagnostic test for pregnant patients with suspected PE [35]. A normal perfusion scan and negative CTPA appear to be equally safe in ruling out PE in pregnancy [34]. As a result, the 2019 European Society of Cardiology (ESC) guidelines on acute PE suggest that perfusion scintigraphy or CTPA (with a low-radiation-dose protocol) should be considered, to rule out suspected PE during pregnancy, and that CTPA should be considered as the first line option if the chest radiograph is abnormal [34].

Diagnostic algorithms for PE in pregnancy

Until recently, diagnostic algorithms (including clinical prediction rules with D-dimer measurement) that have been used for years to rule out PE in non-pregnant patients have not been validated in pregnant women, due to the exclusion of pregnant women from high-quality prospective clinical management studies and trials [34]. Moreover, D-dimer levels rise throughout pregnancy [32]. Due to these limitations, diagnostic imaging has until recently continued to play a crucial role in establishing or excluding diagnosis of PE in pregnancy. The imaging studies, although improved by more modern techniques, still expose the mother and fetus to radiation. Therefore, it has for some time been hypothesised that, if a pregnancy-adapted algorithm was available to safely avoid diagnostic imaging in pregnant women with suspected PE, it would be invaluable [36].

Addressing this crucial research priority, a multicentre multinational academic prospective clinical management study evaluated a pregnancy-adapted algorithm. This assessed three criteria from the "YEARS" algorithm which had previously been validated in non-pregnant patients. These criteria include 1) clinical signs of DVT, 2) haemoptysis, and 3) PE as the most likely diagnosis, along with risk-adapted D-dimer cut-offs. The primary outcome was recurrent VTE at 3 months [36]. According to the diagnostic algorithm, PE was deemed excluded if none of the three YEARS criteria were met, and the D-dimer level was <1000 $ng \cdot mL^{-1}$, or if one or more of the criteria were met, and the D-dimer level was <500 $ng \cdot mL^{-1}$. Where PE was not excluded, patients underwent CTPA, unless a thrombosis was identified on CUS in

women with clinical signs of DVT. 498 pregnant women with suspected PE were included. At baseline, 20 patients were diagnosed with PE (4.0%). Using this algorithm, CTPA was avoided in 195 women (39%, 95% CI 35–44%). The proportion of women in whom PE could be excluded was higher in the first trimester and lowest in the third trimester, and imaging was avoided in 65% of patients in the first trimester, compared to only 32% in the third. During follow-up, a popliteal DVT was diagnosed in one patient (0.21%, 95% CI 0.04–1.2%) and no patient at 3 months experienced PE, suggesting the efficacy of this algorithm in ruling out PE during pregnancy [36], and as reflected in current ESC guidelines [34].

Similarly, a multicentre multinational prospective management outcome study for the diagnosis of PE in pregnancy was conducted in 11 centres between France and Switzerland over 8 years from 2008 to 2016. This study included 395 women who presented to emergency departments with clinically suspected PE. PE was excluded in patients with low or intermediate clinical probability and negative D-dimer test. All other patients underwent lower limb CUS and, if negative, CTPA; if CTPA was inconclusive, a ventilation/perfusion scan was performed. If the following diagnostic workup was negative, PE was excluded, and untreated women were scheduled for follow-up at 3 months. Using this diagnostic strategy 28 (7.1%) women were diagnosed with PE, and 367 were excluded. Among untreated women after exclusion of PE, the rate of symptomatic VTE events at follow-up were 0.0%. Therefore, one can conclude that a diagnostic strategy involving clinical assessment, D-dimer measurement, CUS and CTPA can safely rule out PE in pregnant women [37]. While negative CUS alone was not enough to exclude PE, the 2019 ESC guidelines recommend that if symptoms or signs are suggestive of DVT then CUS should be carried out and, if it is positive, therapeutic treatment should be continued without the need for additional imaging modalities [34].

Treatment/management of VTE in pregnancy

In order to ensure safe and timely management, PA-VTE should be managed by an experienced multidisciplinary team, involving (but not limited to) such specialities as haematology, obstetrics, anaesthesia and cardiology [38]. Ideally, written care pathways should be discussed with and agreed by the woman who has experienced the VTE event [17]. The standard treatment of VTE in pregnancy is anticoagulation with LMWH (although the optimal dose has not been defined in high-quality studies). LMWH is preferred to UFH due to the lower risk profile and more predictable pharmacokinetics. Both LMWH and UFH do not cross the placenta, nor are they teratogenic, unlike other anticoagulants such as vitamin K antagonists and direct oral anticoagulants (DOACs) [38].

DOACs are contraindicated in pregnancy: aside from being shown to cross the placenta in animal studies, they have been insufficiently studied, and their human reproductive risks are unknown [39]. Fondaparinux is a synthetic anticoagulant that is similar to heparins. Fondaparinux appears to cross the placenta in small quantities [39]. While there are fewer available safety data compared to LMWH, a review of 65 pregnancies where fondaparinux was used suggested that the drug was well tolerated, with pregnancy complication rates similar to the general population [40]. However, it is important to recognise that many published results reporting successful fondaparinux use involve exposure in the second trimester or later [39]. As such, it is not routinely recommended, and given its unknown fetal risk, avoidance in the first trimester is urged if possible [38].

Once VTE is suspected, treatment with LMWH should be immediately initiated. VTE in pregnancy is, in general, classified as provoked and is thus usually treated for a finite duration of anticoagulation (although individual risk assessment is crucial, as the optimal duration of anticoagulation is not supported by high-quality data). Anticoagulation is indicated for a minimum of 3 months (and for at least 6 weeks postpartum). The European guidelines on acute PE in women, and a recent consensus statement from the ESC on PE optimal follow-up, suggest that after PE provoked by hormones (pregnancy), indefinite anticoagulation is not warranted, particularly if bleeding risk is high and no risk factors for recurrent VTE are present [41]. However, close attention should be paid to additional, perhaps persistent, risk factors (including antiphospholipid syndrome) during personalised shared decision-making. Moreover, an evaluation should be conducted after 3–6 months (following initial more intense follow-up) following a PE, in particular to ensure that an indication of chronic thromboembolic disease (CTED) and, subsequently, CTEPH does not exist [34, 38]. The management of LMWH during the peripartum period for women diagnosed with VTE during pregnancy is not supported by high-quality data [17]. The incidence of spinal haematoma after regional anaesthesia is uncertain [17]. Guidelines suggest delaying regional anaesthesia for at least 24 h after a therapeutic LMWH dose, assuming normal renal function and absence of extremes of body weight. Again, individual planning is very valuable [34, 38]. There is a paucity of data surrounding the optimal timing of postpartum LMWH re-initiation, and this should be guided by a personalised risk assessment, with consideration for the mode of delivery and thrombotic *versus* bleeding risks [17]. The 2019 ESC guidelines recommend that "LMWH should not be given for

⩾4 h after removal of the epidural catheter; the decision on timing and dose should consider whether the epidural insertion was traumatic, and take into account the risk profile of the woman" [34].

Long-term VTE sequelae

In addition to representing a leading cause of maternal mortality and immediate morbidity, PA-VTE can also result in long-term morbidity from PTS [42]. PTS is a frequent and disabling complication of DVT and reduces quality of life, with patients frequently seeking medical advice and treatment [43]. PTS is believed to occur following DVT as a result of venous hypertension. Mechanisms contributing to this venous hypertension include 1) persistent venous obstruction and valvular reflux, and 2) inflammation leading to delayed thrombus resolution and induction of vein wall fibrosis [43]. Symptoms may include leg pain, heaviness, fatigue and swelling, where the intensity tends to progress over the course of the day, and signs ranging from leg oedema/skin changes to recurrent thromboses and ulceration [42, 43]. Apart from the aforementioned implications for maternal health, PTS is also associated with considerable cost to society, *i.e.* it is costly as measured by health resource utilisation, direct costs and indirect costs [44].

In the Norwegian venous thrombosis in pregnancy (VIP) study, 313 women with pregnancy-related VTE and 353 controls naïve for VTE at the time of index, across 18 hospitals from the years 1990–2003, were identified in order to examine the long-term outcome of pregnancy-related VTE. Years later, in 2006, they completed a comprehensive questionnaire that included a self-reported Villalta score as a measure of PTS, where a score of ⩾5 represented some degree of PTS. Ultimately excluded were 39 cases and four controls. This study identified 204 patients as having experienced a DVT in the lower limb, and 70 with PE. Based on these patients' Villalta scores, 42% of women with lower limb DVT, 24% with PE and 10% of the controls were diagnosed with PTS, 3–16 years later. Of these women, 7%, 4% and 1%, respectively, reported severe PTS (Villalta score ⩾15) [45]. In this study, proximal postpartum DVT was found to be the strongest predictor for the development of PTS, and advanced age and smoking were independently associated with PTS [45]. Women with PTS had a significantly lower disease-specific quality of life (assessed with a quality of life/symptom questionnaire (VEINES-QOL/Sym), score 36.5), when compared to cases without PTS (score 52.3) and controls (score 52.8). The quality of life/symptom questionnaire VEINES-QOL/Sym (part of the VEnous INsufficiency Epidemiological and Economic Study) was included in the initial questionnaire [45]. The prevalence of PTS in PA-VTE has not been evaluated in prospective studies [6].

In the case of PE, CTEPH is a potentially fatal late sequela [34]. Normally the patency of the pulmonary arterial bed is restored in PE survivors within a few months; however, in some cases the thrombi become persistent and organised, resulting in an obstructing vasculopathy. Clinical symptoms of CTEPH may resemble those of acute PE or pulmonary arterial hypertension [34]. While evidence on the association between a pregnancy associated with PE and subsequent CTEPH is still lacking, a large prospective cohort study observed a CTEPH incidence of 3.8% after an acute first episode of PE [46]. Future pregnancy in the setting of CTEPH continues to confer a high maternal mortality and is thus considered to be contraindicated; CTEPH therefore demands prompt and effective diagnosis [47]. Meanwhile, some patients may present with normal pulmonary haemodynamics at rest, despite symptomatic disease [34]. When this is present, and other causes of exercise-induced limitations are excluded, this is characterised as CTED. Identification of patients with CTED in the absence of pulmonary hypertension is crucial and should be conducted in expert CTEPH referral centres, as medical therapy is not indicated [34].

Osteoporosis following anticoagulation in pregnancy was reported in older studies, where treatment with UFH was more frequently used. Some of these studies report osteoporosis in as many as 3% of women. However, during more recent decades, LMWH has almost completely replaced the use of UFH, with an associated very low risk of osteoporosis and osteoporotic fracture [6]. A large retrospective study including 1267 pregnancies managed with the LMWH tinzaparin reported osteoporosis in only 0.2% of women. Notably, all women who experienced osteoporosis had additional contributing risk factors including low body mass index, treatment with corticosteroids, pre-existing osteoporosis and smoking [48].

Evidence limitations and research priorities

Evidence-based guideline recommendations for thromboprophylaxis in pregnancy are based largely on observational studies and extrapolated from data in non-pregnant patients. This lack of high-quality data specific to pregnancy results in a lack of consistency amongst recommendations. This ultimately has led to a number of decisions regarding LMWH prophylaxis that are likely to be value and preference sensitive [39]. Therefore, a systematic approach to VTE prevention needs to be adopted. This question is currently being addressed in a higher-VTE-risk group of pregnant women by the ongoing Highlow academic randomised

controlled trial (RCT) (ClinicalTrials.gov identifier NCT01828697), which aims to determine optimal VTE prevention strategies for women with prior VTE, comparing a fixed low dose of LMWH with an intermediate weight-adjusted dose of LMWH in pregnant women with previous history of VTE and an indication for ante- and postpartum thromboprophylaxis. Furthermore, the ongoing pilot PARTUM (Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity) RCT aims to determine the feasibility of a full RCT comparing 6 weeks of treatment with low-dose aspirin and placebo for postpartum women with VTE risk factors [17].

In addition, current recommendations for thromboprophylaxis during pregnancy and the postpartum period are based on guidelines from predominantly western populations [8]. Therefore, along with an urgent need for more high-quality data, there is also a crucial need to include more racially diverse populations: guidelines are currently being implemented in populations who are poorly represented in studies driving guideline recommendations [8]. Moreover, while it is thought that the risk of VTE increases in the presence of multiple risk factors, data are lacking on how individual risk factors interact [17].

Currently, there is a paucity of data on long-term outcomes after PA-VTE, as cohort studies monitoring long-term complications have never been conducted in this population, with present evidence being based on data from a few observational studies [6]. As such, further research is required in order to assess the long-term risk of PTS, pregnancy outcome, and recurrent thrombosis after PA-VTE, in order to guide continued follow-up and management.

Conclusions

Pregnant women are at a higher VTE risk than the general population. VTE risk assessment is crucial (in early pregnancy, when risk factors change and at delivery/postpartum) in order to identify women who may benefit from VTE risk-reduction strategies. Optimal VTE risk-reduction strategies are currently poorly defined; however, ongoing high-quality RCTs will address this crucial knowledge gap. Diagnosis of VTE may be challenging; however, recently published prospective clinical management studies have impacted on guidelines surrounding diagnosis of PE during pregnancy. Knowledge gaps remain; however, multidisciplinary care of pregnant women with a diagnosis of VTE in pregnancy is essential and can positively impact on women's experiences and potentially improve outcomes.

Key points

- VTE is a leading cause of maternal morbidity in the developing world.
- Women with an inherited thrombophilia or personal VTE history are at greatest risk for a PA-VTE.
- LMWH is the pharmacological agent of choice for antenatal and postnatal thromboprophylaxis and treatment.
- It is suggested that more than two thirds of women's VTE-related deaths could be prevented with improvements to care.

Self-evaluation questions

1. During which period of pregnancy and the puerperium is the daily risk of VTE greatest?
2. Women with what risk factors are at highest risk for VTE recurrence during pregnancy?
3. For how long does the pregnancy-induced prothrombotic state persist?
4. What are the pitfalls of thromboprophylaxis during pregnancy?
5. List the modern advances in computed tomography technology that have significantly reduced radiation exposure to mother and fetus.
6. How long is anticoagulation indicated for as treatment?

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Suggested answers

1. The daily risk of VTE is greater in the postpartum period, with the greatest risk being evident in the first 6 weeks after delivery.
2. Women at highest risk are those with a history of unprovoked or hormone-provoked VTE.
3. The pregnancy-induced prothrombotic state persists until 6 weeks postpartum.
4. The pitfalls of thromboprophylaxis during pregnancy include cost, inconvenient and painful administration, risk of bleeding, osteoporosis and HIT.
5. 1) Reducing the anatomical coverage of the scan, 2) using iterative reconstructive techniques, 3) reducing the kilovoltage, and 4) reducing the contrast-monitoring component of the CTPA.
6. Anticoagulation is indicated for a minimum of 3 months, and for at least 6 weeks postpartum.