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Review Article

Management of venous thromboembolism in pregnancy

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ABSTRACT

Venous thromboembolism (VTE) in pregnancy, consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major factor of maternal mortality. Several patient-specific risk factors along with the physiologic changes of pregnancy promote a state of hypercoagulability in pregnant women. Detailed assessment of all pregnant women can establish a risk profile that would guide clinical decisions, and balance potential therapeutic benefits with side effects. Differentiating between physiologic changes of pregnancy and symptoms of VTE can be challenging and warrants meticulous clinical evaluation. Timely and accurate diagnosis of VTE with proper imaging is essential for its management, and systemic anticoagulation remains the cornerstone of VTE prevention and therapy. Furthermore, advanced invasive treatment options such as inferior vena cava filters and thrombectomy can be considered for complex cases. Importantly, the risk of systemic anticoagulation should be balanced against the risk of VTE-associated morbidity and mortality for mother and fetus, and an informed decision should be made. In this review, we present an up-to-date overview of VTE management in pregnancy and the postpartum period.

1. Introduction

Pregnancy and puerperium are well-established risk factors for venous thromboembolic disease (VTE) [1]. During pregnancy, the risk of VTE is about 5-fold compared to non-pregnant women, and becomes 30 to 60-fold at postpartum [2]. Deep vein thrombosis (DVT) events are more frequent during pregnancy, while pulmonary embolism (PE) events are more likely to occur at the postpartum period [3]. DVT is associated with adverse obstetric outcomes and is a significant contributor to maternal morbidity (e.g., increased frequency of post-thrombotic syndrome in pregnant women) and mortality [4]. PE, as a result of DVT, is the leading cause of maternal mortality in the United Kingdom and Ireland, and it ranks sixth in the United States [5,6]. Therefore, the effective prevention and management of VTE and its complications are crucial [7]. However, accurate VTE diagnosis in this population is inherently challenging due to the physiological changes of pregnancy and the potential risks that some of the diagnostic imaging methods may pose to the developing fetus. Therapeutics decisions should be made after thorough balancing of the risks and potential benefits of each strategy for the mother and fetus. In this review, we offer an up-to-date overview of VTE management in pregnancy and puerperium.

2. Pathophysiology of VTE in pregnancy

Pregnancy is associated with the gradual development of a hypercoagulable state with a physiologic increase in clotting factors such as von Willebrand factor, fibrinogen, and factors II, VII, VIII, IX, and X,

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from conception to delivery. Notably, fibrinogen levels rise to 50% [8]. These physiological changes, while aiming to facilitate hemostasis after delivery, affect prothrombin time (PT) and partial thromboplastin time (PTT), and could complicate the anticoagulation monitoring of pregnant women. The hyperestrogenic state of pregnancy leads to decreased activity of protein S, which normally interacts with protein C to inactivate Factors Va and VIIIa directly, via decreased production, and indirectly via increasing C4b binding protein [9,10]. Furthermore, increased levels and activity of thrombin-activated fibrinolysis inhibitor, plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2 inhibit fibrinolysis. The three most important factors leading to venous stasis and venous hypertension during pregnancy parturition and puerperium are: (i) decreased venous tone mediated by endothelial mediators such as nitric oxide that is upregulated by estradiol and vasodilatory prostaglandins such as PGI2, (ii) compression of inferior vena cava and iliac veins by the gravid uterus and, (iii) endothelial injury to pelvic veins during delivery [11,12].

3. Risk factors for VTE in pregnancy

Pregnant women exhibit a 2-fold higher risk for VTE in the first two trimesters and progress to a 9-fold higher risk in the early postpartum period compared to non-pregnant women [3,13]. Most postpartum VTE cases are attributed to thrombophilia and Cesarean section delivery [14]. Preeclampsia is another factor that increases the risk for postpartum VTE [15]. Pregnant women with a personal past medical history of VTE are at higher risk for developing pregnancy-associated VTE. Therefore, it is recommended that women with a history of both provoked or unprovoked VTE or first-degree relatives who have a history of inherited thrombophilia should be evaluated for antiphospholipid syndrome and other inherited thrombophilias including factor V Leiden (FVL) and prothrombin G20210A gene variant (PT G20210A), as well as antithrombin III, protein C, and protein S deficiencies. The population identified as high risk (history of VTE, thrombophilia) should receive a prophylactic or intermediate dose of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) antepartum and postpartum [16]. Women with recurrent pregnancy loss or stillbirth should be tested for antiphospholipid syndrome, which increases the risk of pregnancy-associated VTE by 5%–12% [17,18]. Assisted reproduction methods elevate VTE risk by 2- to 3-fold during the first trimester, due to exposure to high estradiol levels [19]. Other risk factors for pregnancy-related VTE include maternal age >35, nulliparity, multiple gestations, gestational diabetes, antepartum hemorrhage, hypertension, smoking and obesity [14].

4. Diagnosis of DVT in pregnancy

Timely and accurate diagnosis of DVT in pregnancy is imperative because if left untreated it can progress to PE, which can be detrimental for mother and fetus. DVT is more common in pregnant women as compared to non-pregnant women. Nonetheless, contrary to the general population where DVT originates mostly in the calf and progresses proximally, in pregnant women DVT arises mostly from the proximal veins of the left lower limb (79% from iliofemoral veins) [20,21]. DVT diagnosis can be challenging as some of its clinical manifestations (i.e. lower extremity edema, pelvic and back pain) mimic pregnancy-associated symptoms. Well-established clinical prediction tools for DVT in the general population, such as Wells' criteria and modified Geneva score have limited use in pregnant women [22,23]. A clinical prediction tool for pregnant women in the first trimester has been proposed by Chan et al. to facilitate DVT diagnosis. It includes three clinical parameters: (i) left lower extremity symptoms, (ii) difference in calf circumference of more than 2 cm and (iii) presentation in the first trimester, collectively called the LEFt rule. The LEFt rule can be used in cases where the initial diagnostic work-up with compressive ultrasound (CUS) is equivocal [24]. The use of D-dimers to guide diagnostic decisions in pregnancy is limited due to their physiologic increase during pregnancy, especially during second and third trimesters [25]. The sensitivity of D-dimers varies according to threshold from 94% (cut-off 500 ng/ml) to 90% (cut-off 1000 ng/ml). Nonetheless, testing of serial levels of red blood cell agglutination D-dimer, a method for high-sensitive D-dimer testing, has been evaluated in the SimpliRED prospective cohort study as a diagnostic tool to exclude DVT in pregnancy. This method is known as high-sensitive D-dimer testing. SimpliRed had a high negative predictive value, which according to Chen et al. could reach 100% (81 of 81 patients) for the exclusion of DVT in pregnant women [26]. Notably, there was a low DVT prevalence in the study population [24]. Another ongoing prospective clinical study aims to evaluate the combined use of the LEFt rule along with D-Dimer testing to accurately exclude DVT in pregnant women (NCT02507180).

Fig. 1 depicts the diagnostic flowchart for VTE in pregnancy. Initial assessment of suspected DVT in symptomatic pregnant women involves CUS with color flow doppler [27]. Ultrasound imaging is preferable because it is risk-free for both mother and fetus, low cost, and readily available at the point-of-care. CUS diagnostic accuracy is high in cases of symptomatic femoropopliteal DVT in the general population (sensitivity: 97%, specificity: 94%). However, in pelvic vein thrombosis (most common in pregnant women), CUS is hindered by the anatomical location of iliofemoral veins and the size of the gravid uterus. CUS combined with the Valsalva maneuver, and with evaluation of venous flow changes with respiration increases the sensitivity for the diagnosis of iliac vein DVT in pregnancy [28]. Recent guidelines on the management of venous thromboembolism in pregnant women from the American Society of Hematology suggest that lower limb CUS for investigation of suspected DVT should include the iliac veins and should be followed by serial imaging if the initial examination is negative or equivocal [29]. In pregnant women with suspected iliac vein thrombosis, the diagnostic process should be supplemented by magnetic resonance venography if the initial CUS is negative. In cases where compression ultrasound is negative, but clinical suspicion of DVT is high, the diagnostic workup should continue with reassessment on days 3 and 7 with high-sensitive D-dimer testing (if available) and/or repeat CUS. CT venography could be considered in cases of suspected pelvic DVT. The above diagnostic tool with a mean estimated fetal absorbed dose of 25 mGy (under the threshold for fetal risk) should be avoided as it bears the risks of congenital anomalies and growth and mental retardation to the developing fetus [30]. Instead, magnetic resonance venography is a reliable alternative with high diagnostic accuracy in cases of pelvic thrombosis, without any radiation exposure to mother and fetus [31]. Protocols without gadolinium can be considered, as fetal gadolinium exposure (in supraclinical doses) has been associated with developmental abnormalities in small animal models, while evidence in humans is lacking [22]. The use of magnetic resonance venography for DVT diagnosis is uncommon in daily practice due to its limited availability at the point-of-care [32].

5. Diagnosis of PE in pregnancy

The most common non-specific symptoms of PE (i.e. shortness of breath, tachycardia and chest pain), overlap with physiologic changes during pregnancy. Therefore, laboratory workup, diagnostic imaging, patient history, and physical examination are necessary for the accurate and timely diagnosis of PE in pregnancy. The pulmonary embolism rule-out criteria (PERC rule), which are used in the general population to rule-out PE in patients with low pre-test probability for PE, is inadequate in pregnant women [33]. In a prospective study, the pregnancy-adapted YEARS algorithm was assessed to safely rule out PE without the need for computed tomography angiography (CTA). The YEARS algorithm includes three criteria: (i) clinical signs of DVT, (ii) presence of hemoptysis, and (iii) PE as the most likely diagnosis. PE was safely ruled out and anticoagulation therapy was deferred without CTA imaging if none of the three criteria were met, and D-dimer levels were <1000 ng/ml, or

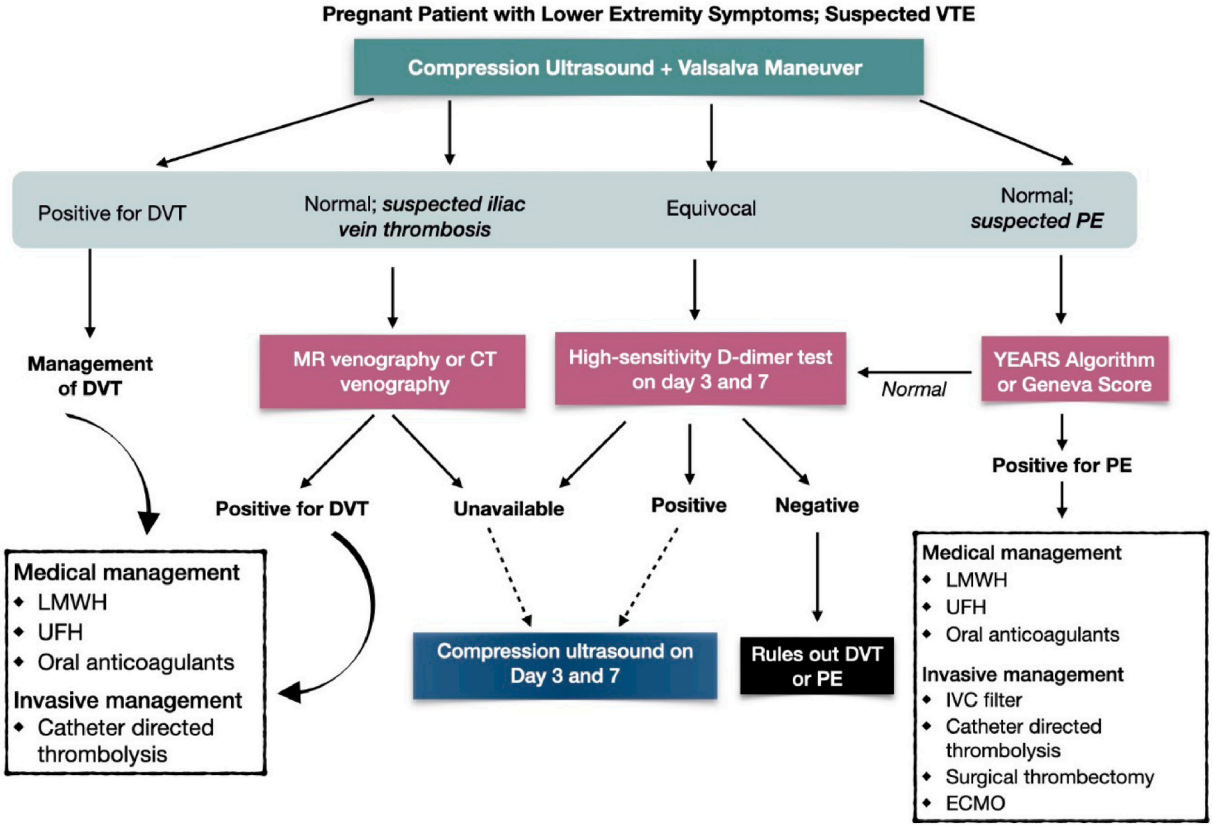

Fig. 1. Diagnostic flowchart of VTE in pregnancy [34].

if one or more of the three criteria were met and D-dimer <500 ng/ml [34]. The use of the YEARS algorithm to reliably exclude PE in pregnant patients was further supported by the findings of another group that retrospectively assessed 371 pregnant women, 77 of which met the criteria for PE exclusion according to the YEARS algorithm, and none of these patients was diagnosed with PE during the initial work-up or 3-month follow-up [35]. Similarly, Righini et al. used the Geneva score with D-dimer to rule-out PE without imaging, thus avoiding the possible side effects of radiation and/or intravenous contrast exposure [36]. However, a recent retrospective secondary analysis of the Diagnosis of Pulmonary Embolism in Pregnancy (DiPEP) study concluded that the accuracy of YEARS algorithm or Geneva score with D-dimer testing to rule-out PE was lower than expected [37]. The YEARS and Geneva D-dimer methods that rule out PE without imaging would have not recognized 5 out 12 and 3 out of 12 women diagnosed with PE by the DiPEP secondary analysis, where an imaging study was used as a diagnostic gold standard. Van der Pol's group contested the findings of this study due to (i) lack of strict adherence to the YEARS criteria (ii) altered D-dimer levels due to administration of anticoagulation, (iii) lack of definitive diagnosis of PE confirmed by imaging [38]. The clinical importance of these differences is not clear and should be addressed in future trials. Therefore, these nuances should be considered when clinicians utilize the YEARS and Geneva/D- dimer methods to rule out PE in pregnancy [34].

Another recent development was a new version of the Geneva score (Pregnancy-Adapted Geneva Score or PAG Score) [39]. The authors reported high discriminative power to identify patients with a low, intermediate, or high score, associated with the increasing prevalence of PE, 2.3%, 11.6%, and 61.5%, respectively while the ROC curve was 0.795 for the PAG Score compared to 0.684 for the Geneva score [39].

The optimal imaging strategy should balance the following factors: (i) missed or delayed diagnosis of PE is associated with significant morbidity and mortality for mother and fetus, (ii) erroneous use of systemic anticoagulants in case of a false-positive diagnosis exposes the mother and fetus to a significant risk of bleeding. Fig. 1 summarizes the diagnostic flowchart for PE in pregnancy. Since PE originates primarily from underlying DVT, CUS is the first investigation of choice in symptomatic patients. In case of negative CUS, chest x-ray follows in routine clinical practice, although its sensitivity to detect PE is limited [32]. However, chest X-ray can still be useful in the workup of those patients and can help differentiate from other entities such as pleural effusion, atelectasis or parenchymal opacities [40]. RCOG guidelines support chest x-ray as the initial test in obstetric patients presenting with symptoms suggestive of PE [41]. However, this practice is contested by recent studies [40]. Computational tomography pulmonary angiography (CTPA) or V/Q scan, which are widely used to diagnose PE in the non-pregnant population, are debatable as the first choice of test in pregnant women. Regarding exposure of mother and fetus to radiation, studies have considered CTPA and V/Q scan safe for the diagnosis of PE in pregnancy and puerperium [42]. CTPA is more expensive and associated with higher radiation exposure to the mother (especially to the proliferating breast tissue) than to the fetus. V/Q scan is a diagnostic alternative with low radiation exposure (2.5 mSv compared to 8–20 mSv in CTPA) and high sensitivity (97% compared to the CTPA 86%). Additionally, the V/Q scan is free of contrast-related side effects [43]. Neither of the two modalities has been associated with a significant increase in the risk of breast cancer [44]. CTPA is the preferred imaging modality for PE diagnosis in pregnancy, especially in the US [45]. The American Thoracic Society has suggested the GRADE system (Grades of Recommendation, Assessment, Development, and Evaluation), which recommends any pregnant patient with suspected PE and signs of lower limb DVT undergo CUS. If signs of DVT are absent in CUS, chest X-ray should follow. Patients with a normal or equivocal chest x-ray, but with suspected PE should be considered for a V/Q scan. CTPA is reserved as the last imaging work-up for pregnant patients with equivocal or normal V/Q scans [46]. Magnetic resonance pulmonary angiography (MRPA)

has potential advantages over CTPA for the diagnosis of PE. Contrast-enhanced MRPA is free of ionizing radiation and provides accurate structural and flow mechanics information [47]. Gadolinium's potential effects in pregnancy have been discussed in the section "Diagnosis of DVT in pregnancy". MRI using motion resistant techniques (i.e. steady-state free precession), which do not require contrast administration are being studied for pregnant women. One study found that this contrast-free MRPA technique had comparable results to gadolinium-enhanced scans regarding adequate visualization of all the central and lobar pulmonary arteries, and 90% of the segmental pulmonary arteries [48].

In conclusion, since the diagnosis of VTE in the pregnant population is highly challenging, validated clinical algorithms should guide clinical judgment for optimal detection of the disease.

6. VTE prophylaxis in pregnancy

The core principles of VTE prevention in pregnant and postpartum women are similar, despite the differences in recommendation and strategies suggested by different organizations. Every clinical decision should be based on a detailed, documented risk assessment of the VTE risk of each pregnant woman in early pregnancy, upon modification of any of the risk factors and postpartum. Several VTE risk scores have been devised to guide clinical decision-making [49], some of which have demonstrated clinical significance in guiding appropriate thromboprophylaxis [50,51], and reducing the incidence of VTE [51]. Nevertheless, all of these reports contain limitations in methodology and should be critically assessed by the practicing physician. Even though individual studies have demonstrated that effective thromboprophylaxis prevents VTE in the obstetric population [52,53], a systematic review reported a lack of evidence to support these recommendations [54].

6.1. Low molecular weight heparin

By consensus, the recommended agent of pharmacological VTE prophylaxis in pregnant patients is LMWH. LMWH is delivered subcutaneously and safely administered to pregnant and breastfeeding populations [55]. Clinical recommendations suggest the utilization of low prophylactic or half-therapeutic dose schemes for VTE prophylaxis in pregnant and postpartum women [16,56]. An ongoing clinical trial (NCT 01828697), has been set to answer the question of optimal dosing, comparing a fixed dose of LMWH versus a weight-adjusted dose in terms of VTE prevention. Table 1 summarizes dosing recommendations for anticoagulant prophylaxis and treatment of VTE in pregnancy.

6.2. DOACs

Evidence of direct oral anticoagulant agents (DOACs) safety for use in VTE prevention in pregnant women is lacking. Nevertheless, the American College of Obstetricians and Gynecologists suggests that DOACs could be considered for thromboprophylaxis in postpartum non-breastfeeding women [16].

6.3. Anti-platelets

The use of aspirin in pregnancy has been extensively studied in the context of antiphospholipid syndrome (APS) and recurrent pregnancy loss (RPL). Several clinical trials and meta-analyses have demonstrated that the combination of LMWH with aspirin improves birth outcomes but has no effect on maternal VTE incidence and severity, in patients with a history of APS/RPL [57–63]. It is recommended that these women with APS/RPL are treated with both low-dose aspirin prophylactic-dose and LWMH. The prophylactic role of aspirin in the pregnant population without APS is being investigated in the PARTUM randomized controlled trial (Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity, NCT04153760) which evaluates low-dose aspirin in the prevention of postpartum VTE. While strong evidence is available for thromboprophylaxis in high-risk pregnant women, optimal prevention of VTE in women with other recognized risk factors is not well supported [54,64]. Evidence to support mechanical thromboprophylaxis (compression devices e.g. thromboembolic deterrent stockings, pneumatic compression devices) in the obstetric patient is limited [65]. As a result, mechanical thromboprophylaxis is usually reserved for cases where pharmacological thromboprophylaxis is contraindicated [66]. The heterogeneity of evidence has generated substantial variation in VTE prophylaxis guidelines [67,68]. In the United Kingdom, many VTE risk factors are considered for the decision of pharmacological thromboprophylaxis of obstetric patients [66]. On the contrary, in North America, pharmacological thromboprophylaxis is uniformly recommended only for patients at the highest risk of VTE [16,29,56]. This heterogeneity of approaches underpins the need for prospective, carefully designed clinical trials to evaluate and establish optimal strategies for the effective prevention of VTE. Considering the scarcity of evidence-based directives, personalized decision-making that incorporates the patient's preference should be followed.

7. VTE management in pregnancy and postpartum period

Systemic anticoagulant therapy is the preferred treatment option for most cases of VTE and should be started upon diagnosis. Treatment of VTE in pregnancy requires at least 3 months of anticoagulant therapy (optimally 6 months including the puerperium period) [69]. LMWH and unfractionated heparin reduce mortality and recurrence of VTE and are the suggested treatment options in pregnancy [16]. However, LMWH is more convenient to use in the outpatient setting. Table 1 summarizes dosing recommendations for VTE treatment in pregnancy.

8. Low molecular weight heparin (LMWH)

LMWH does not cross the placenta and has not been linked with fetal hemorrhage or teratogen effects on the developing fetus [16]. It is the

Table 1
Heparin prophylaxis and therapeutic dosing for VTE in the obstetric population [16].
FDA: US Food & Drug Administration; h: hours; PPT: partial thromboplastin time; Da: Dalton.

		FDA pregnancy category	Half-life	Molecular weight (Da)	Prophylaxis	Treatment
Unfractionated heparin		C	0.5-2 h	15,000	3 × 5000 Units/day 2 × 7500 Units/day	Iv; PPT 60–80 s
Low molecular weight heparin	Certoparin	B	4.6 h	5600	1 × 3000 Units/day	2 × 8000 Units/day
	Dalteparin	B	2–2.3 h	5000	1 × 5000 Units/day	1 × 200 Units/kg/day 2 × 100 Units/kg/day
	Enoxaparin	B	4.5 h	4500	1 × 40 mg/day	2 × 1 mg/kg/day
	Nadroparin	C	3.7 h	4300	1 × 2850 Units/day	2 × 90 Units/kg/day
	Tinzaparin	B	3.3–3.5 h	6500	1 × 3500 Units/day	1 × 175 Units/kg/day
	Fondaparinux	B	17-21 h	1728	1 × 2.5 mg/day	1 × 5 mg/day (<50 kg) 1 × 7.5 mg/day (50–100 kg) 1 × 10 mg/day (>100 kg)
	Danaparoid	B	25 h	6000	2 × 750 Units/day	Iv; anti-Xa level 0.5–0.80 IU/ml

treatment of choice in pregnant women due to its tolerability and convenient dosing profile that does not require routine monitoring [29]. Compared to UFH, LMWH is superior in reducing thrombotic complications, major bleeding, and death. It has similar efficacy in reducing VTE recurrence and equal risk for all-cause bleeding and a lower risk of heparin-induced thrombocytopenia (HIT) [70,71]. Therefore, it is the preferred anticoagulant for pregnant patients with GFR > 30 ml/min [29,72,73]. Of note, most data for the use of LMWH in pregnancy is derived from studies in non-pregnant patients despite the altered pharmacokinetics of the drug in pregnant women. Overall, anti-Xa monitoring has not improved treatment outcomes [29]. However, it should be considered in specific occasions such as recurrent VTE under anticoagulation therapy, treatment of obese patients, or patients with renal insufficiency [74,75]. In these cases, peak anti-Xa levels are determined 4–6 h after dose administration and the dose is titrated to achieve a level of 0.6 to 1.2 U/ml. Therapeutic levels of anti-Xa are monitored every 4–6 weeks after dose modification [16].

LMWH is well tolerated by pregnant women. The most common adverse effect is local bruising and skin irritation at the injection site. If the skin reaction is severe, or causes discomfort, substitution with another LMWH or a non-heparin anticoagulant (fondaparinux, danaparoid) can be considered [16]. HIT is an uncommon complication in pregnant women under treatment with LMWH (frequency < 0.1%). According to guidelines, monitoring of platelet count is not required in pregnant patients without additional risk factors for HIT [76]. In HIT cases, the preferred anticoagulant is danaparoid (transplacental passage has not been documented) [56]. Although fondaparinux lacks conclusive evidence regarding transplacental passage and potential risks to the developing fetus, some studies have suggested that it crosses the placenta in small amounts, therefore, it should be avoided during the first trimester [77].

9. UFH

UFH has been used in the past for thromboprophylaxis and the treatment of VTE. UFH is preferred in pregnant patients with renal impairment (GFR < 30 ml/min). UFH can also be considered transitional therapy prior to delivery or surgery because it offers better management of heparin's half-life and rapid reversal of anticoagulation effects. It can be administered intravenously or subcutaneously and dosing needs weight-adjustment [29].

10. Oral anticoagulants

Vitamin K antagonists (warfarin, acenocoumarol) cross the placenta and have been associated with fetal abnormalities, especially between the 6th and 12th week of pregnancy, when the fetus is most vulnerable to vitamin-K deficiency [78]. Vitamin K antagonists reduce the synthesis of vitamin K-dependent proteins that are essential for normal fetal development and increase the risk for fetal malformations such as bone, central nervous system and ocular abnormalities [79]. Furthermore, their use in the first trimester is associated with an increased potential for fetal loss and an increased risk for fetal cerebral hemorrhage during delivery [80,81].

Direct oral anticoagulants (DOAC) (Dabigatran, Rivaroxaban, Apixaban, Edoxaban) have largely substituted the use of Vitamin K antagonists in the treatment and prevention of VTE [29]. Their safety profile in pregnancy has not been studied thoroughly in humans [82,83]. Animal studies have documented their cross-placenta transfer and their presence in breastmilk [84,85]. In a study of 223 pregnant women, DOAC exposure was associated with congenital abnormalities in 7/137 neonates [69]. Therefore, the use of DOAC in pregnant women and in women trying to conceive is currently contraindicated [86].

11. Treatment considerations pre- and post-delivery

LMWH should be ceased 24 h prior to scheduled delivery. Alternative treatment regimens that ensure a shorter half-life of heparin or transition to UFH could be considered. Transition to UFH can be considered up to 36 h before delivery and stopped 4–6 h before delivery to facilitate normalization of anti-Xa level [16,87,88]. After delivery, anticoagulation can be reinstated 6–12 h after vaginal delivery, 12–24 h after uncomplicated cesarean section or 24 h after epidural catheter removal [89]. Notably, the highest VTE risk is observed at 2 weeks postpartum. Therefore, anticoagulant therapy should be continued for a minimum of 6 weeks postpartum to permit for a total treatment duration of at least 3 months [90–92]. Several randomized trials that compared 3-month to >6-month duration of therapy identified that the latter did not lower risk of VTE recurrence, while patients experienced a 2.5-fold increase in major bleeding events [92]. Moreover, a meta-analysis of individual patient data from randomized trials that attempted to compare, treatment of 3 months compared with >6 months revealed that although anticoagulants are effective at preventing VTE recurrence while patients are on therapy, the risk of recurrence is comparable after cessation of therapy [93].

LMWH or UFH are acceptable options for continued treatment postpartum. Alternative options include fondaparinux or warfarin. Evidence on the effects of these anticoagulants in neonatal bleeding is limited. Nevertheless, their use is considered safe for the newborn based on the results of observational studies [94]. DOAC safety profile has not been studied thoroughly in breastfeeding women, therefore they are not recommended as treatment [85,95].

12. Advanced treatment options

Anticoagulant therapy is adequate for most cases of VTE in pregnancy. However, in cases of massive PE (acute PE accompanied by systemic hypotension, pulselessness, or persistent bradycardia with signs/symptoms of shock) advanced therapies are required [96]. These therapies include systemic thrombolysis, surgical thrombectomy, catheter-directed thrombectomy/thrombolysis, or extracorporeal membrane oxygenation (ECMO) [29]. Catheter-directed thrombolysis or thrombectomy is an option for patients with limb-threatening proximal DVT. Advanced treatment options can also be considered in cases with sub-massive PE (manifesting with right ventricular dysfunction or myocardial necrosis without hypotension) [96].

13. Thrombolysis

Systemic thrombolytics such as tenecteplase and alteplase are molecules that promote the conversion of plasminogen to plasmin and facilitate the degradation of fibrin molecules [97]. Thrombolysis can promptly improve patient's hemodynamic status and symptoms and increase survival. Additionally, thrombolysis limits damage to the right ventricle and lowers the possibility of another PE [97]. However, the potential benefits come at the cost of increased bleeding risk (intracranial hemorrhage, major bleeding, or fatal hemorrhage) and possible placenta-related adverse effects (placental abruption, premature labor, fetal demise) [97–99]. Transplacental passage of tissue plasminogen activator and streptokinase is negligible and has not been linked with fetal coagulopathy or other malformations [99–101]. Based on a few cases of thrombolysis used for VTE in pregnancy, a literature review reported 2.8% (4/141) deaths of pregnant women and 1.4% (2/141) neonatal deaths [102]. The mortality rate of thrombolysis used for the treatment of PE in non-pregnant patients was found to be 2.17% (23/1061), in a recent meta-analysis [102,103]. A meta-analysis of studies on the use of systemic thrombolysis in antepartum and postpartum women reported a 28.4% risk for major bleeding (primarily vaginal hemorrhage or intra-abdominal bleeding depending on the mode of delivery) [98,104].

Thrombolytic agents can be administered through a multi-side-hole catheter that is advanced intravascularly to the site of the thrombus. This method is known as catheter-directed thrombolysis and has the theoretical advantages of lower bleeding risk and no transplacental passage of the lytic agents since they are delivered directly into the thrombus [105,106]. Catheter-directed thrombolysis seems to offer the advantage of lower risk for bleeding compared to systemic thrombolysis, although more data is needed for confirmation [5]. This technique can be combined with mechanical methods of clot retrieval such as aspiration thrombectomy (direct aspiration of thrombus from the vein using a catheter, a device or a sheath), balloon maceration (fragmentation of thrombus using an angioplasty balloon), balloon angioplasty (dilation of the venous lumen using inflating a catheter-bound balloon) with or without stent placement (deployment of a metallic endoprosthesis to scaffold the dilated venous lumen) [107].

14. Inferior vena cava (IVC) filters

IVC filter placement is considered in cases where anticoagulation therapy is contraindicated, ineffective (recurrent VTE on full-dose anticoagulation therapy), or not well tolerated because of complications such as heparin-induced thrombocytopenia, heparin allergy or significant bleeding during anticoagulation therapy [108]. Their placement involves exposure of mother and fetus to ionizing radiation, which could adversely impact the early stages of fetal development, therefore, it should be avoided unless the benefits clearly outweigh risks. Proposed techniques to limit radiation exposure to fetus include using a lead abdominal shield and intravascular ultrasound guidance for IVC filter placement. IVC filters have been successfully deployed through the jugular or femoral access without impediment by the gravid uterus in all trimesters of pregnancy. Infrarenal placement has been associated with compression by the gravid uterus and possible displacement that can lead to migration or fracture of the filter or endothelial damage to IVC. On the contrary, suprarenal placement offers the advantages of accelerated venous flow (from the convergence of blood flow from renal veins) which can facilitate the lysis of thrombi and protect from thrombi originating from the ovarian veins. Therefore, it is the preferred method of IVC filter placement [108]. Theoretically, retrievable filters are an attractive option for pregnant patients, due to their young age and transient hypercoagulable state. Of note, a randomized control trial in non-pregnant patients treated with IVC filter for proximal DVT, suggested that the long-term presence (8 years) of IVC filters is associated with an increased risk for DVT and has no survival benefit [109]. In a study of retrievable IVC filters in pregnancy, the overall complication rate was 25% and rate of successful removal was 81%.

Complications related to IVC filter placement include threatened preterm labor, leg swelling and retroperitoneal hematoma. Other reported complications are DVT (including filter and IVC thrombosis), filter occlusion, tilt, fracture, filter migration and failed retrieval [108,110]. To date, no randomized clinical trials have assessed the effectiveness and risks of IVC filter placement in pregnancy, therefore, IVC filters should be considered for the same absolute indications as in non-pregnant population, ideally, by a multidisciplinary team of experts.

15. Other invasive VTE treatment options and supportive measures

Surgical thrombectomy, percutaneous catheter thrombectomy, extracorporeal membrane oxygenation (ECMO) are other invasive treatment options available for VTE in pregnancy and puerperium. In a series of 127 pregnant or peripartum women with massive PE, 36 were treated with surgical thrombectomy, 7 were treated with percutaneous catheter thrombectomy and 3 were treated with ECMO and anticoagulation. Patients treated with surgical thrombectomy had a survival rate of 86%, major bleeding rate of 20%, fetal death rate of 20% and premature delivery rate of 8%. Percutaneous catheter thrombectomy was associated with a survival rate of 100%, major bleeding rate of 20% and fetal death rate of 25%. In 2/7 women, this method was insufficient and led to escalation with other treatments (ECMO or surgical thrombectomy). ECMO for 4–10 days was used in 3/127 cases. All patients survived without any major bleeding and there was one documented premature delivery [104]. Due to the lack of randomized clinical trials and a small number of patients included in this case series, this data should be used cautiously. Nevertheless, percutaneous and surgical thrombectomy could be viable alternatives to thrombolysis, especially early postpartum, to avoid the risk of massive postpartum hemorrhage related to thrombolytic therapy. These procedures should be conducted in specialized centers with available supportive measures (cardiopulmonary by-pass), by skilled medical professionals.

16. Conclusion

The physiologic changes associated with pregnancy and the postpartum period raise the risk of VTE. VTE and its complications are major causes of maternal and fetal morbidity and mortality. Therefore, prompt and effective identification of women who will benefit mostly from preventive anticoagulation is of paramount importance. VTE diagnosis in pregnancy can be optimized following an algorithmic approach where CUS has a central role. MR and CT venography, D-dimers and serial CUS are integral parts of the algorithm. When PE is suspected, an X-ray, CTPA and V/Q scan can help establish the diagnosis. Prevention and treatment decisions in the obstetric population are challenging because of the limited data regarding the safety and efficacy of anticoagulants in such patients and the critical time for the developing fetus. The primary anticoagulation choice in pregnancy is LMWH and should be administered for a minimum of 3 months. Advanced treatments such as thrombolysis, IVC filters and mechanical methods of thrombus removal can be associated with significant fetal morbidity and mortality and should be considered under special circumstances such as failure of other treatments, massive or sub-massive PE, or acute limb-threatening DVT. Overall, decision-making should be supported by guideline recommendations, careful consideration of benefits and risks for the mother and the developing fetus, availability of resources and level of expertise, and the patient's ethical code and preference.

Declaration of competing interest

The authors have no conflict of interest to declare. All authors have accepted the contents of manuscript submitted.

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