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REVIEW

Venous Thromboembolism in Pregnancy: Challenges and Solutions

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Abstract: Venous thromboembolism (VTE) is a serious medical condition that can lead to severe morbidity and mortality, making it a significant public health concern. VTE is a multifactorial condition that results from the interaction of genetic, acquired, and environmental factors. Physiological changes during pregnancy increase the risk of VTE as they express Virchow's triad (increased coagulation factors, decreased fibrinolysis, trauma, and venous stasis). Moreover, pregnancy-related risk factors, such as advanced maternal age, obesity, multiple gestations, and cesarean delivery, further increase the risk of VTE. Managing VTE in pregnancy is challenging due to the complexity of balancing the risks and benefits of anticoagulant therapy for both the mother and the fetus. A multidisciplinary approach involving obstetricians, hematologists, and neonatologists, is necessary to ensure optimal outcomes for both the mother and baby. This review aims to discuss the current challenges associated with VTE in pregnancy and identify potential solutions for improving outcomes for pregnant women at risk for VTE.

Keywords: venous embolism, thrombosis, pregnancy, VTE, anticoagulation

Introduction

Venous thromboembolism (VTE) is a significant pregnancy complication, with an incidence of approximately 1 per 1000 pregnancies (reported incidence; 0.025% to 0.1%).[1,2] Despite advances in diagnostic and therapeutic approaches, VTE remains a leading cause of maternal mortality in developed countries. In the United States, VTE is responsible for approximately 10% of maternal deaths, with pulmonary embolism (PE) being the most common cause. In the CDC's pregnancy-related mortality surveillance, PE accounted for 20% of pregnancy-related deaths between 1991 and 1999, surpassing other complications associated with pregnancy, such as infection, hemorrhage, and pregnancy-induced hypertension.[3] However, it is essential to note that when VTE is diagnosed exclusively based on a clinical evaluation, the incidence of the disease may be overestimated. Nonetheless, an analysis of 395,335 pregnant women in a retrospective case-control study at 24 weeks of gestation found the incidence of VTE to be 85 per 100,000 pregnancies,[4] while in a community-based study over 30 years, 200 women per 100,000 person-years were diagnosed with VTE, and DVT was three times more common than PE.[5] European countries have observed similar trends.[5,6] Based on a retrospective study of more than 72,000 deliveries, the incidence of DVT was 0.71 per 1000 births (95% CI 0.5–0.9), of which 0.5 (95% CI 0.33–40.66) occurred antenatally and 0.21 (95% CI 0.11–31) following delivery.[7] According to the same study, PE occurred 0.15 times per 1000 deliveries (95% CI 0.06–0.24), with 0.07 cases (95% CI 0.01–0.13) occurring before and 0.08 (95% CI 0.02–0.14) after the delivery.[7] Regarding the antepartum period, data about VTE are somewhat conflicting, with some studies observing a higher incidence in the second and third trimesters.[8–10] In contrast, others observe similar risk of VTE during all three trimesters of pregnancy.[11–14] A consensus exists that the risk of VTE is highest in the postpartum period, with the incidence peaking in the first six weeks following delivery.[9] The incidence of VTE varies according to

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different population groups and risk factors. For example, the incidence of VTE is higher in women with a history of VTE or thrombophilia, those undergoing assisted reproductive technology, and those with medical comorbidities such as diabetes or hypertension.[9,15] Furthermore, racial and ethnic disparities have been reported in the incidence of VTE during pregnancy, with African American women being at a higher risk than White caucasian women.[16]

Given the relatively high incidence of VTE during pregnancy, the associated morbidity and mortality, and the difficulty in diagnosis, it is crucial to understand the risk factors and pathophysiology that form the current challenges of VTE in pregnancy. This knowledge can inform clinical practice and guide the development of evidence-based approaches to prevent and manage VTE in pregnant women. This review article provides a comprehensive overview of the current knowledge regarding VTE in pregnancy, emphasizing the clinical challenges of diagnosis and treatment and the most up-to-date clinical strategies to address them. By synthesizing current evidence-based knowledge and identifying gaps in understanding, this review aims to provide a valuable resource for healthcare providers and researchers working to improve outcomes for pregnant women at risk for VTE.

Pathophysiology

Physiological Hypercoagulable State During Pregnancy

Virchow's triad is converged—endothelial trauma, venous stasis, and hypercoagulability—during pregnancy and postpartum (Figure 1). Normal pregnancy is accompanied by hypercoagulability and hypofibrinolysis. These changes in the coagulation and fibrinolytic systems aim to reduce intrapartum blood loss but, at the same time, inadvertently increase the

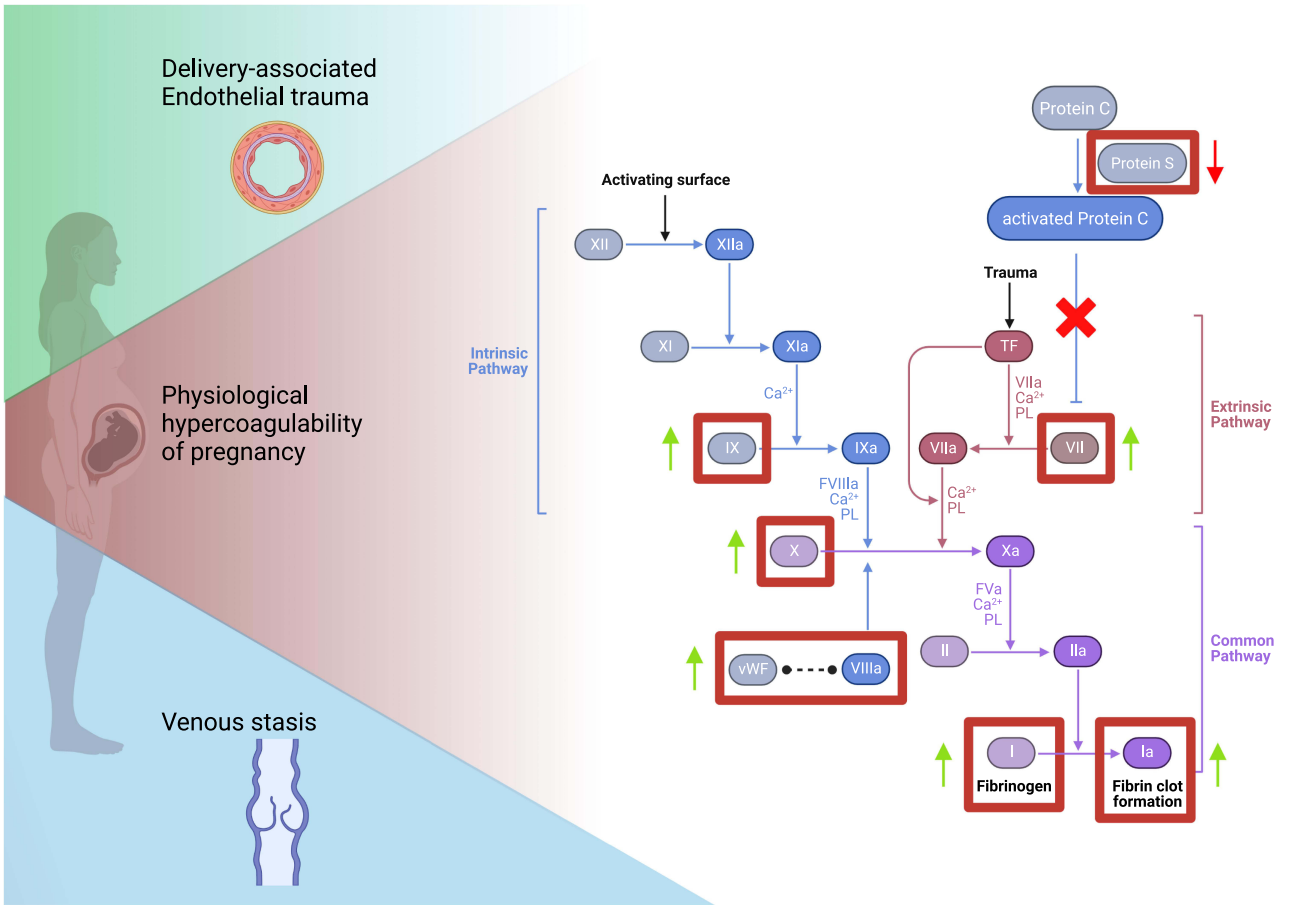

Figure 1 Convergence of Virchow's triad during pregnancy —endothelial trauma, venous stasis, and hypercoagulability—as well as postpartum. Coagulation is gradually activated to prepare the mother for delivery. The anticoagulant activity of protein S is reduced, and activated protein C resistance rises. A higher concentration of fibrinogen, factors V, IX, X, and VIII, enhances procoagulant activity, leading to increased thrombin production, as demonstrated by an increase in soluble fibrin and prothrombin levels. Reduced fibrinolysis results from increased plasminogen activator inhibitor type 1 and 2 and decreased tissue plasminogen activator (tPA) activity. Endothelial damage to the pelvic vessels results from mechanical stress during normal, induced, or operative vaginal delivery. Venous stasis occurs due to the combination of estrogen-induced venodilation, pelvic venous compression, and compression of the left iliac vein by the right iliac artery.

risk of thromboembolism. The coagulation system during pregnancy is physiologically activated due to increased procoagulant factors and the decrease or inactivation of anticoagulant and fibrinolytic systems. Factors VII, VIII, X, XII, von Willebrand factor, and fibrinogen increase.[17] Notably, factor VII reaches very high levels increasing as much as tenfold,[18] while fibrinogen levels at term are 200% higher than before pregnancy.[19] In addition, a significant decrease in the level of physiological anticoagulants is observed, manifested as diminished protein S activity and acquired resistance to activated protein C.[17] Furthermore, there is a reduction in fibrinolytic activity due to an increase in both plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor type 2 (PAI-2).[20]

Platelet function is also altered during pregnancy. Platelets decrease in number but are more responsive to agonists, such as adenosine diphosphate (ADP) and thrombin, leading to increased platelet aggregation.[21] This may be in part due to changes in their surface receptors.[22] Finally, placental trophoblastic cells release nanoparticles that have been shown, in vitro, to exert prothrombotic effects on platelets and the vascular endothelium.[23] The enhanced platelet aggregation further increases the risk of thrombosis, which, combined with the reduction in fibrinolytic activity, results in the formation of fibrin clots more resistant to degradation. In addition to the changes in the coagulation system and platelet function, pregnancy is also associated with alterations in hormonal homeostasis and hemodynamics. Pregnancy hemodynamic changes are characterized by increased intravascular volume and reduced systemic vascular resistance.[24] An increase in estrogen, progesterone, and relaxin during pregnancy causes systemic vasodilation and increased venous capacitance,[25] which increases vessel diameter and decreases blood flow velocity as observed by real-time and duplex Doppler ultrasound.[26] This hemodynamic state favors the stasis of blood in the venous circulation. Mechanical obstructions further aggravate the venous pooling due to the gravid uterus compressing the iliac veins and compromising the venous return.[27] This, combined with prolonged immobility, such as bed rest or prolonged sitting or standing, commonly seen during pregnancy, further increase the thrombotic risk.[28,29] The elevation in estrogen and progesterone levels can also decrease antithrombin activity and increase clotting factors synthesis,[30] activate the hypoxia-inducible factor-1 pathway,[31,32] and result in hypercoagulability and platelet activation and aggregation.[30] Finally, the vessel wall structure is also altered during pregnancy, with an increase in the number of smooth muscle cells and a decrease in elastin content which render the vessel wall prone to injury and subsequent thrombosis.[33]

It is becoming apparent that in conjunction with the overall hypercoagulable state, increased vascular compliance, venous stasis, mechanical compression of the pelvic veins, and delivery-associated endothelial damage complete Virchow's triad of hypercoagulability, stasis, and vascular damage creating a highly thrombogenic environment, even during normal, uncomplicated pregnancy.

Thrombophilia in Pregnancy

Thrombophilia refers to inherited or acquired conditions that may increase the risk of thrombosis during pregnancy, leading to VTE. Thrombophilia, which occurs in 8–15% of Caucasians, is the second most common risk factor for pregnancy-related VTE (with a history of VTE being the first).[34] There are two main types of thrombophilia – acquired and inherited thrombophilia (IT). The inherited forms are due to genetic mutations affecting genes implicated in the coagulation cascade. Several ITs have been associated with an increased risk of VTE during pregnancy, including factor V Leiden, prothrombin gene mutation, and deficiencies of Antithrombin, protein C, and Protein S.[35] ITs are relatively rare in the general population. For instance, Factor V Leiden, the most common IT in the Caucasian population, has a prevalence of approximately 5%.[36] The mutation resists the anticoagulant effects of activated protein C, leading to a prothrombotic state. Prothrombin G20210A gene mutation is another common IT, occurring in approximately 2% of the general population. It results in the overproduction of prothrombin, a precursor of thrombin, leading to thrombotic conditions, such as VTE and PE.[37] Deficiencies of Antithrombin, protein C, and protein S are ITs that are relatively rare but associated with a high risk of VTE during pregnancy and recurrent pregnancy loss.[35,38] Antithrombin is a natural anticoagulant that inhibits thrombin and other coagulation factors, while protein C and protein S are cofactors in the inactivation of coagulation factors. Deficiencies in any of these factors lead to a prothrombotic state, with the risk of VTE during pregnancy increased by up to 30-fold.[39] According to their absolute risk for initial and recurrent venous thromboses, thrombophilias may be categorized into high, moderate, and low. Antithrombin III deficiency, protein C deficiency, and protein S deficiency are considered high-risk thrombophilias, moderately risk thrombophilias include

factor V Leiden, prothrombin gene mutations, factor VIII deficiency, and low-risk thrombophilias encompass factor XI, factor IX, and hyperhomocysteinemia.[40]

Furthermore, additional criteria such as the zygosity of the mutation and prior personal or family history significantly influence the risk for VTE in pregnancy.[35] As more of those criteria are met, the risk of thrombosis increases. For instance, the risk of VTE in pregnant women heterozygous for factor V Leiden without a personal history of VTE or an affected first-degree relative is estimated not to exceed 5–10 per 1000 deliveries. In contrast, the risk increases to up to 10% if a personal history of VTE is present,[15,41,42] and up to 15/1000 deliveries with an affected first-degree relative.[15,41] Finally, homozygous pregnant women without a personal history of VTE or a first-degree relative affected by VTE are at a 1–2% risk, whereas those with a history have a 17% risk.[41]

In addition to inherited thrombophilias, acquired thrombophilias can also increase the risk of VTE during pregnancy. Antiphospholipid syndrome (APS) is the most common cause of pregnancy-acquired thrombophilia.[43] Recently, studies have provided further insight into the pathogenesis of APS. Vascular thrombosis is associated with antiphospholipid (APL) antibodies in this syndrome. Specifically, anticardiolipin and lupus anticoagulant antibodies were most commonly found to be associated with thromboembolic events.[44,45] A 2:1 ratio of venous-to-arterial thrombosis characterizes APS, and thrombosis tends to be recurrent. VTE, specifically deep venous thrombosis of the legs, is the most common manifestation and recurrence of APS.[46] It has been reported that 76% of recurrences will also be venous if the initial thrombotic event is venous.[46] The hypercoagulable state of pregnancy compounds the risk of thrombosis to the extent that over half of the thrombotic episodes in patients with APS are related to pregnancy or combined oral contraceptives.[47] Some studies have shown that many pregnant APS patients still experience thrombotic episodes despite receiving thromboprophylaxis.[48,49] Diagnosing thrombophilias during pregnancy can be challenging, as many of the laboratory tests used to diagnose these conditions are affected by pregnancy-related changes in hemostasis.[50] However, identifying women with thrombophilias is important, as it can inform decisions about prophylactic anticoagulation during pregnancy and postpartum. Women with a personal or family history of VTE or a strong family history of thrombophilia should be screened for inherited thrombophilias before or early in pregnancy. Women with a history of recurrent pregnancy loss or fetal death may also be candidates for screening for antiphospholipid syndrome.

Diagnosis and Management

Clinical Presentation and Diagnostic Workup of VTE in Pregnancy

VTE in pregnancy can present in various ways, ranging from asymptomatic to life-threatening events such as massive pulmonary embolism (PE) with hemodynamic instability. Several symptoms that raise suspicion for VTE in non-pregnant women, including mild tachycardia, tachypnea, dyspnea, and lower extremity edema and pain, are nonspecific and common during a routine, uncomplicated pregnancy. Consequently, physical examination is often insufficient for diagnosing VTE. In the case of DVT in pregnancy, the two most common presenting symptoms are pain and swelling. These symptoms may or may not be associated with erythema, warmth, and lower extremity tenderness. It is estimated that 80% of pregnant women who suffer from DVT experience these symptoms, but the diagnosis is frequently missed.[14] While pregnancy-related DVTs are almost identical to those seen in non-pregnant women, there is a greater prevalence of left-sided DVTs (70% to 90%) involving the proximal and iliac veins during pregnancy.[12,51] A possible explanation for this phenomenon may be the enhanced venous stasis due to compression of the left iliac vein by the right iliac artery and compression of the inferior vena cava by the gravid uterus.[12,52] Symptoms of PE in pregnant women include palpitations, dyspnea, and movement-exacerbating chest pain and present a diagnostic challenge for clinicians since many of these symptoms are caused by benign conditions that are common during pregnancy, such as pregnancy-related physiological dyspnea, gastroesophageal reflux disease, or discomfort caused by the gravid uterus. A clinician's threshold for conducting imaging in this population should be low, given the recognition that PE can also present with similar symptoms and is a significant cause of maternal mortality.

According to clinical guidelines, several diagnostic modalities are available for diagnosing VTE in pregnant women.[53,54] When DVT is in the differential, whole leg ultrasound (US) (Compressing the femoral to the popliteal vein and visualization of the iliac veins) should be considered.[54] If DVT is detected by compression maneuvers from the femoral to the popliteal vein or a thrombus is visualized in the iliac vein, DVT is diagnosed, and appropriate therapy should be initiated. If the whole leg US is

negative, DVT is excluded, and patients can be followed clinically. In case of equivocal US results or if high suspicion remains despite non-visualization of thrombi in the iliac vein, Magnetic Resonance Imaging (MRI) can be considered.[55,56] When a pregnant patient presents with symptoms suspicious of PE, a careful assessment of risk factors for PE should be obtained. Without risk factors and routine physical examination, other likely diagnoses should be considered. In a moderate-high PE suspicion case, the definite diagnosis of PE requires either one of two imaging modalities that involve radiation, a Ventilation-perfusion (VQ) scan, or Computed Tomography Pulmonary Angiography (CTPA).[54] It is recommended to conduct bilateral leg ultrasounds with iliac visualization before either test, as the presence of DVT may make further testing unnecessary, avoiding ionizing radiation. If a VQ scan yields a typical result, PE would be excluded, whereas a PE diagnosis is made if it produces a high probability result. If the VQ scan is non-diagnostic, a CTPA should be performed. As with the VQ scan, a normal CTPA test would exclude disease, while a positive test would confirm the diagnosis. If the CTPA is ambiguous or non-diagnostic, a similar approach can be taken by performing a VQ scan or repeating the CTPA test.[54] Finally, the place of D-dimer testing for diagnosing or excluding VTE in pregnancy is currently equivocal. Although "normal" D-dimer values have been well described for various assays in asymptomatic pregnant women, the cut-points below which PE can be safely excluded in symptomatic pregnant women have not been established. The current state of research does not allow us to determine whether PE can be safely excluded in patients with average D-dimer results and a non-high clinical probability. On the contrary, several case reports have established that D-dimer levels in pregnant women with radiologically confirmed PE have been below non-pregnant cut-points.[57–59]

Pharmacological and Non-Pharmacological Management of VTE in Pregnancy

The treatment of VTE in pregnancy is particularly challenging, as the safety of anticoagulant drugs and their potential adverse effects on the developing fetus must be carefully considered.[60] Anticoagulant therapy is the mainstay of treatment for VTE in pregnancy. The choice of anticoagulant agent depends on several factors, including the location and severity of the thrombosis, the gestational age, and the potential for adverse effects on the fetus. Among the anticoagulation options are low-molecular-weight heparins (LMWHs), unfractionated heparins (UFHs), and Warfarin which should be used postpartum only. LMWHs are preferred over UFH as the first-line treatment for preventing and treating VTE in pregnancy.[53,61,62] Randomized trials have shown that LMWHs are equally or more effective than UFH in non-pregnant women.[63,64] LMWHs are excreted in breast milk at a minimal level, so they pose no risk to breastfeeding infants.[65] Moreover, compared with UFH, LMWHs exhibit less risk of adverse effects, including hemorrhage, heparin-induced thrombocytopenia, osteoporosis, and allergic reactions.[62] It is recommended that pregnant women avoid Warfarin. Warfarin crosses the placenta and increases the risk of severe complications, such as miscarriage, stillbirth, developmental abnormalities, neurological disorders, and excessive bleeding.[66] However, Warfarin can be used while breastfeeding. UFH is administered by continuous intravenous or subcutaneous injection, while LMWH is administered by subcutaneous injection. The initial dose of UFH is calculated based on the patient's weight and adjusted according to the activated partial thromboplastin time (aPTT). In contrast, the dose of LMWH is based on the patient's weight and administered twice daily without monitoring. Currently, treatment durations for pregnancy range from three to six months, including six weeks after delivery[66,67] The use of long-term (ie, extended period over 12 months) anticoagulation is advised for women with antiphospholipid antibody syndrome or two or more thrombophilias that also have VTE[68] and for women with any thrombophilia and history of recurrent thromboses.[69] In addition to anticoagulant therapy, non-pharmacological interventions can also manage VTE in pregnancy. Compression stockings can help reduce the risk of post-thrombotic syndrome and alleviate leg swelling and pain symptoms. They should be worn during the day and removed at night.[70,71] Moreover, early and frequent ambulation is encouraged and can help prevent venous stasis and reduce the risk of VTE. Bed rest should be avoided unless necessary.[70] IVC filters can be considered in patients with recurrent VTE despite anticoagulant therapy or in those with contraindications to anticoagulant therapy;[70] however, their use should be carefully weighed against the potential risks and benefits.[72] Finally, thrombolytic therapy involves administering drugs that dissolve blood clots (eg, tissue plasminogen activator and streptokinase) and restore blood flow, which is considered a last-resort treatment. A significant concern with thrombolytic therapy during pregnancy centers on the effects it has on the mother (ie, major hemorrhage) and on the placenta (ie, premature labor, placental abruption).[73] It has been reported that thrombolysis can be successfully performed during pregnancy without causing harm to the fetus, but there are limited reports of these cases, and most involve streptokinase.[74–76] Therefore, available guidelines recommend thrombolytic therapy in pregnancy only for life-threatening issues (eg, PE with refractory cardiorespiratory compromise).[77]

Pregnant women with VTE require close monitoring to assess treatment response, prevent recurrent VTE, and manage potential complications. The frequency and type of monitoring depend on several factors, including the severity of the VTE, the kind of anticoagulant used, and the fetus's gestational age.[10] In general, pregnant women on anticoagulation therapy should have regular monitoring of their coagulation parameters, as well as regular fetal monitoring to assess fetal growth and well-being. In addition, pregnant women with VTE should receive education on the signs and symptoms of recurrent VTE and be advised to seek prompt medical attention if they experience any new or worsening symptoms.[78]

Challenges

Challenges in History

Identifying High-Risk Pregnancies

It is well established that pregnancy is associated with an increased incidence of VTE due to various mechanisms, as mentioned above. Thus, identifying high-risk women is crucial for decreasing the incidence of VTE in pregnancy and reducing fetal and maternal mortality (Table 1).

Table 1 Risk Factors Associated with Pregnancy-Associated VTE

Antepartum Risk Factors	**Adjusted OR**
Immobilization	
BMI < 25 kg/ m	7.7 (3.2–19)
BMI > 25 kg/ m	62.3 (11.5–337)
Smoking	2.1 (1.3–3.4)
Twins	2.6 (1.1–6.2)
Assisted reproduction	4.3 (2–9.4)
IBD	2.1 (1.7–2.7)
Diabetes	3.5 (1.1–11)
Varicose veins	2.2 (1.6–4.8)
Hyperemesis	2.5 (1.4–4.5)
Postpartum Risk factors	
Cesarean Delivery (non-emergent)	1.3 (0.7 −2.2)
Cesarean Delivery (emergent)	2.7 (1.8–4.1)
Postpartum infection	20.2 (6.4–63.5)
Immobilization	
BMI< 25 kg /m2	10.8 (4–28)
BMI > 25 kg/m2	40.1 (8–201)
Postpartum bleeding	4.1 (2.3–7.3)
Preeclampsia	3.1 (1.8–5.3)
Smoking	3.4 (2–5.5)
IBD	2.6 1.8–3.7
Varicose veins	3.9 2.6–5.9

Note: Data from[79,96]

Pregnancy-related risk factors for VTE include preterm birth,[81] preeclampsia,[81] cesarean delivery,[81] assisted reproductive technology,[81] stillbirths,[81,82] obstetric hemorrhages,[81,82] and postpartum infection.[81,83] Peripartum-associated comorbidities predisposing for VTE include diabetes mellitus,[81] systemic lupus erythematosus,[84] inflammatory bowel disease,[81] and sickle cell disease.[85,86] Obesity is not consistently associated with antepartum VTE, but postpartum thrombosis occurs at higher rates in patients with BMI above 35 who also present concurrent mobility problems and decreased functional capacity.[79,81–83]

One logical approach is to classify risk factors as weak or moderate based on the postpartum or peripartum period. Moderate risk factors (OR 2–9) include thrombophilia and previous venous thromboembolism, while weak risk factors include bed rest (> three days) and varicose veins (OR <2).[87] In addition to those mentioned above, factors previously reported to increase the risk of postpartum VTE include age >35 years, cesarean section, blood group A, hypertension, and postpartum bleeding.[4] In an extensive registry originating from Australia, stillbirth (aOR 5.97), lupus (aOR 8.83), and transfusion (aOR 8.84) were most strongly associated with PE in postpartum. In contrast, age ≥ 40 years (aOR 1.67), parity ≥ 3 (aOR 1.49), pregnancy hypertension (aOR 2.06), and preterm live birth (aOR 2.18) were associated to a lesser extent.[1]

Special Populations

Women with Prior History of VTE

According to existing literature, a prior history of thrombosis is one of the most significant risk factors,[15] particularly when unprovoked. Pabinger et al found that 4 of 65 women (6.1%) without thromboprophylaxis experienced VTE compared with 5 of 73 women (6.9%) who had received prophylaxis.[42] In a cohort of 88 women with a previous episode of VTE who became pregnant at least once without receiving antithrombotic prophylaxis, 120 peripartum periods without prophylaxis were recorded with a postpartum VTE recurrence rate of 8.3%.[88]

Cesarean Delivery

Many independent VTE risk factors previously confounded the association between cesarean delivery and VTE. In large cohorts, as the Australian registry and the study of Abe et al, cesarean section carried an increased risk regardless of whether it was conducted in the presence (aOR 3.7) or absence (aOR 3.11) of labor after adjusting for confounders.[1,89] In the Norwegian study, however, uncomplicated cesarean delivery was not associated with an increased risk after complication adjustment.[83] It remains unclear if a cesarean section is associated with a higher incidence of VTE or if this can be attributed to the reasons leading to a cesarean section or underlying complications, such as extensive blood loss or infection.

Assisted Reproduction

Ovarian stimulation results in a hyperestrogenic state. Similarly to the combined oral contraceptive pill or hormone replacement therapy, exogenous estrogens have been associated with hypercoagulability and VTE.[90,91] Studies suggest that oestradiol levels correlate with fibrinogen, D-dimers, and activated protein C (APC) resistance.[92] Furthermore, ovarian stimulation is associated with increases in several circulating coagulation factors; factor V, fibrinogen, von Willebrand factor, increased coagulation activation markers; prothrombin fragment 1 + 2 and D-dimers, and impairment of endogenous anticoagulants; decreased antithrombin and protein S levels.[93,94] As a result, all patients should be individually assessed for their risk of thrombotic complications before having IVF, considering thrombophilias, previous VTE, family history of VTE, concurrent medical conditions, increased age (>40 yrs), or obesity.

Antiphospholipid Syndrome

Antiphospholipid syndrome is defined by venous or arterial thrombosis and specific pregnancy complications with persistently positive tests for antiphospholipid antibodies. It usually warrants long-term anticoagulation after a first thrombotic event because of an increased risk of recurrence. Women with APS receive antenatal therapeutic doses of low molecular weight heparin (LMWH) (those on Warfarin convert to LMWH before six weeks of pregnancy) until after delivery and then change back to oral anticoagulants. However, the optimal management of such women to

prevent recurrent thrombosis is difficult due to the scarcity of relevant data. In the Bauersachs et al study of 28 women, two thrombotic events occurred postpartum despite treatment, highlighting the increased risk.[95] These women require close management and collaboration between experts, including a hematologist. Women not on blood thinners should start LMWH promptly in the first trimester, which should be continued for at least six weeks after delivery. In the presence of antiphospholipid antibodies alone, without APS, RCOG suggests LMWH for seven days postpartum.[96]

Challenges in Physical Examination

Physiological lower extremity edema is expected during the second and third trimesters; consequently, women manifesting symptoms suggestive of deep vein thrombosis (DVT) during the first trimester exhibit a much higher likelihood (odds ratio, 53) of being diagnosed with DVT compared to those who presents symptoms later in pregnancy.[97] It is important to note that pregnant patients may present with atypical symptoms, often involving pain in the thigh or buttock.[79] This is because while the general population suffers from DVTs in smaller and more distally located veins, pregnant individuals demonstrate a slightly increased proportion of DVTs located in iliofemoral vessels (64% vs 54%) and a considerably higher proportion of DVTs isolated to the iliac vein (17% vs 3%), both correlated with increased embolization risks.

Dyspnea, tachycardia, and lower extremity swelling that mimic signs and symptoms of PE are routinely observed in pregnancy due to physiologic changes. Those findings can complicate the assessment of PE presence based solely on clinical factors. Specifically, Varrias et al showed that sinus tachycardia is mainly considered physiologic in pregnancy but is associated with unfavorable outcomes.[98] In the Dipep study, pregnant and postpartum women were tested for PE. Those without PE exhibited similar rates of typical PE symptoms, including pleuritic chest pain (52%), shortness of breath (54%), palpitations (13%), cough (8%), and syncope (5%) relative to women with validated, proving that solely clinical diagnosis of PE in pregnant population is a diagnostic conundrum.[99]

Challenges in Laboratory Findings

D-dimer assays are commonly used in non-pregnant patients to rule out VTE, mainly PE, but the utility of D-dimer among pregnant patients is still debatable One of the concerns is that D-dimer levels increase with gestational age resulting in reduced specificity for VTE[100] (Table 2). Despite previous negative studies advising against it,[101] recent evidence has led the 2019 European Society of Cardiology (ESC) guidelines to recommend considering D-dimer measurement to rule out PE in pregnant or postpartum patients (class IIa, level B).[82,102]

Table 2 The Table Shows How the Following Clinical Criteria Would Perform in 1000 Women, of Whom 65 Had PE as per the DiPEP study

Scores	Sensitivity	Specificity	PPV	NPV
Primary consensus[a]	0.615	0.585	0.093	0.956
Sensitive consensus[a]	0.954	0.035	0.065	0.916
Specific consensus[a]	0.354	0.783	0.102	0.946
PERC[b]	0.677	0.519	0.089	0.958
Simplified Revised Geneva	0.446	0.636	0.079	0.943
Well's (permissive)	0.490	0.617	0.082	0.946
Well's (strict)	0.376	0.895	0.196	0.952
D-dimer (conventional threshold)	0.877	0.088	0.063	0.911
D-dimer (pregnancy-specific threshold)[c]	0.692	0.325	0.066	0.939

Notes: [a]Primary consensus, Sensitive Consensus, and Specific consensus are clinical criteria developed earlier in the DiPEP study to guide advanced imaging decisions for pulmonary embolism in pregnancy and the postpartum period.[103] [c]Previous studies had suggested that using a higher threshold could improve specificity without compromising sensitivity.[114] Data from [99,103,114]

Abbreviation: [b]PERC, Pulmonary embolism Rule-out Criteria.

Challenges in Imaging

Computed Tomography Pulmonary Angiography (CTPA)

In the United States and the rest of the world, CTPA has become the diagnostic imaging standard in non-pregnant patients due to its widespread availability, rapid results provision, and superior sensitivity and specificity for PE compared to ventilation/perfusion (V/Q) scans.[105] One of the contraindications of CTPA is a severe allergic reaction to iodine contrast. CTPA should be performed with caution in patients with severe kidney disease. Although excessive maternal iodine exposure poses a risk for fetal hypothyroidism,[106] contemporary (ie, water-soluble, low-osmolar) iodinated contrast is rapidly cleared from the circulation. Despite initial concerns, it was not associated with severe fetal thyroid dysfunction.[106] Regarding breastfeeding, iodinated contrast does not present a risk to breastfeeding infants, negating postpartum patients' need to "pump and dump" after CTPA.[107] Radiation from diagnostic imaging is an important consideration.

Regarding radiation, the estimated mean fetal doses from CTPA (0.05–0.3 mGy) may be slightly lower than those from V/Q scans (0.17–0.4 mGy). Nevertheless, both are far below the 50 to 100 mGy deterministic threshold for fetal radiation complications and present a minimal estimated risk of excess cancer-related death during childhood (approximately 1/100,000).[108,109] Despite the low risk of ionizing radiation in the fetus, PE imaging may play a role in lifetime attributable maternal cancer risk, mainly because breast tissue is highly radiosensitive during pregnancy.

Although MRI could be considered for diagnosing PE in the general population, magnetic resonance angiography is discouraged due to low sensitivity in the general population. Enhanced MRI is contraindicated peripartum due to the fetal risks associated with gadolinium contrast.[107,110]

Solutions

Lab Testing

D Dimers: Previously, the use of D-dimer testing in pregnant women was limited due to concerns such as (1) limited and inconsistent data on sensitivity and NPV of D-dimer for suspected VTE in pregnancy; (2) absence of pregnancy-specific clinical decision rules to stratify patients according to pretest probability (PTP); (3) unclear appropriate cutoff values for D-dimer tests due to physiological increase during pregnancy. Bellesini et al addressed these concerns, demonstrating high sensitivity and NPV of 99.5% (95% CI, 95.0–100.0; I^2, 0%) and 100% (95% CI, 99.1–100.0; I^2, 0%), respectively, for D-dimer testing. Of note, the single-study estimates for sensitivity and NPV were close to 100%, with low heterogeneity levels. These findings align with the sensitivity observed in the general population, supporting using the D-dimer test to rule out VTE in non-high-risk pregnant women without imaging safely.[111] In contrast, it is essential to mention that the DIPEP study showed very low specificity regardless of the cutoff; thus, D dimer testing could not discriminate between pregnant and postpartum women with or without a PE.[99]

Genetic Testing: Despite extensive efforts to identify high-risk pregnancies using comorbidities, established family risk factors cannot be detected in many families with VTE clustering. Individuals with a first-degree relative with a history of VTE are at increased risk of VTE, almost independent of known heritable risk factors, suggesting the existence of unknown genetic risk factors.[112] Recently, genome-wide association studies on VTE have been published.[113] This would cast some light on genetic causes of pregnancy-associated VTE. In a detailed review regarding the emerging field of non-coding RNAs by Spanos et al, EV-lncRNAs associated with thrombotic risks are identified, among others related to cardiovascular diseases.[114] In the Norwegian hospital case-control study, Dahm et al found new associations between single nucleotide polymorphisms (SNPs): seventeen SNPs and one SNP belonging to the gene encoding P-selectin were associated with postpartum VTE.[115]

Physical Examination

Signs and symptoms of VTE in pregnancy are similar to those in non-pregnant individuals, and they vary between DVT and PE. These include shortness of breath, tachycardia, leg pain or swelling, pelvic discomfort, and chest pain. Shortness of breath is the most common presenting symptom (34.7%), followed by tachycardia (30.4%), leg pain or weakness (9.6%), and chest pain (13%).[116] Thus, it is essential to understand how the accuracy of common symptoms or findings changes during the antepartum or peripartum period. Although there are few validating studies on this population, the DIPEP analysis provided some insight, as presented in the modified Table 3.

Table 3 Diagnostic Accuracy of Presenting Features as Calculated in the Study Population of DiPEP

Symptom/ Sign	Sensitivity	Specificity	PPV	NPV
Presenting feature: Pleuritic chest pain	0.519	0.471	0.407	0.584
Presenting feature: Non-pleuritic chest pain	0.210	0.819	0.447	0.597
Presenting feature: SOB	0.536	0.394	0.382	0.548
Presenting feature: Hemoptysis	0.072	0.961	0.565	0.597
Presenting feature: Cough	0.088	0.911	0.410	0.589
Presenting feature: Syncope	0.050	0.973	0.563	0.594
Presenting feature: Palpitations	0.133	0.884	0.444	0.593
Temperature> 37.5	0.077	0.973	0.667	0.601
Diastolic Pressure < 50 mmHg	0.022	0.992	0.667	0.592
Systolic pressure < 90 mmHg	0.017	0.996	0.750	0.592
O2 saturation <94%	0.149	0.961	0.730	0.618
RR > 24 / min	0.099	0.903	0.419	0.589
Heart rate > 100/min (110/min third trimester)	0.304	0.722	0.433	0.597
Clinical signs of DVT	0.127	0.911	0.500	0.599

Note: Data from Goodacre S, Horspool K, Nelson-Piercy C, et al. The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum. BJOG. 2019;126(3):383–392.[99]

Chan et al created a clinical prediction tool that promises to make the diagnosis of DVT in pregnant women in the first trimester more reliable. 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 workup with compressive ultrasound (CUS) is equivocal.[97]

Imaging

As discussed in detail in the existing literature, lung ventilation/perfusion scintigraphy (V/Q scan) and (CTPA) are widely used to evaluate PE in pregnancy.[82,117] Ventilation/perfusion single photon emission computed tomography (V/Q SPECT) is a promising technique that offers higher sensitivity than planar V/Q and requires a lower radiation dose than CTPA. Despite rapid adoption in other advanced countries, V/Q SPECT remains relatively uncommon in the United States.[118]

Planar lung V/Q scan was a standard test for non-pregnant adults with suspected PE until the turn of the century, and it continues to be a routine test during pregnancy. Guidelines recommend perfusion-only scintigraphy (including half-dose perfusion scintigraphy) in pregnant patients with normal chest radiographs to reduce maternal and fetal radiation exposure.[82,119] Ventilation/perfusion scans are a valuable alternative for patients with CKD or anaphylaxis where CTPA is generally contraindicated. However, they should be avoided in asthmatic patients or patients with severe lung disease. Disadvantages of V/Q scans include limited availability at some centers, longer test completion time, slightly higher fetal radiation dose, and inability to identify alternative diagnoses (ie, if the result is indeterminate or negative for PE).

When transport is an issue in hemodynamically unstable patients, echocardiographic evidence of RV pressure overload strongly suggests the presence of PE in patients with high pretest probability and no other likely causes of RV dysfunction (class I, level C).[82] Both in the general population and in pregnant patients, echocardiographic evidence of RV dysfunction in stable patients contributes to PE severity assessment and assists in clinical decision-making.

Point of care ultrasound (POCUS) has brought a revolution in the diagnostic world, giving the opportunity to clinicians to diagnose dangerous urgent conditions without relying to a radiologist. POCUS may not have an established role in diagnosing PE, although there are signs with decent diagnostic accuracy.[120] Unlike PE, POCUS has tremendous capabilities when it comes to the diagnosis of DVT. There have been numerous studies so far showing that, with the right training, internists, emergency and critical care physicians can match the accuracy of radiologists when it comes to the diagnosis of DVT.[121,122] Serial compression Doppler ultrasonography has the same sensitivity and specificity to exclude

deep vein thrombosis in pregnant women when compared to studies involving men and nonpregnant women, therefore providing a valuable weapon in our diagnostic arsenal.[123]

Advanced Therapies

Most VTE cases in pregnancy will resolve favorably with anticoagulation alone. However, cases of massive PE often times require escalation of care to advanced therapies.[124] These therapies include systemic thrombolysis, catheter-directed thrombectomy/thrombolysis, surgical thrombectomy, or extracorporeal membrane oxygenation (ECMO).[10] Although the existing literature is limited and it remains a conflicting topic, advanced treatment options can also be considered in cases with sub-massive PE (right ventricular dysfunction or myocardial necrosis without hypotension).[125]

Systemic thrombolysis can be used in pregnancy if indicated, as mentioned above. Based on a few cases of thrombolysis in pregnancy, a literature review reported 2.8% (4/141) deaths of pregnant women and 1.4% (2/141) neonatal deaths.[126] Transplacental passage of tissue plasminogen activator and streptokinase is negligible and has not been linked with fetal coagulopathy or other malformations.[127] Although there is no robust data comparing thrombolysis outcomes between pregnant women and the general population, 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).[128]

In the general population, IVC filters are considered when anticoagulation therapy is contraindicated, ineffective (recurrent VTE on full-dose anticoagulation therapy), or not well tolerated because of complications such as heparin-induced thrombocytopenia or heparin allergy.[72] So far, there are no randomized clinical trials to assess the efficacy or risks of IVC filter placement in pregnancy, but in general, there is no mechanistic rationale for suggesting a different approach in pregnancy.

Surgical thrombectomy, percutaneous catheter thrombectomy, and extracorporeal membrane oxygenation (ECMO) are other invasive treatment options for VTE in pregnancy. Out of 127 peripartum women with PE, 36 were treated with classic thrombectomy, 7 with percutaneous catheter thrombectomy, and three were treated with ECMO and anticoagulation. Patients treated with surgical thrombectomy had a survival rate of 86%, a significant bleeding rate of 20%, a fetal death rate of 20%, and a premature delivery rate of 8%. All patients who underwent percutaneous thrombectomy survived (rate of 100%), the major bleeding rate was 20%, and the fetal death rate was 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 significant bleeding, and there was one documented premature delivery.[129] Although this data come from a small sample, it suggests that percutaneous and surgical thrombectomy are noteworthy alternatives to thrombolysis, especially early postpartum, to avoid the risk of massive postpartum hemorrhage as a complication of thrombolytics. Skilled medical professionals should conduct these procedures in specialized centers with available supportive measures (cardiopulmonary bypass).[125]

Multidisciplinary Approach

In the peripartum period, the decision for anticoagulation should be ideally taken with the help of an obstetrician with expertise in thrombosis, an MFM subspecialist, or a "thrombologists." A multidisciplinary team approach is optimal due to the complexity of the condition and the need for sub-specialized care. Massive PE in pregnancy is life-threatening for the mother and the fetus. Therefore, life-saving therapies such as systemic thrombolysis, surgical thrombectomy, catheter-directed thrombectomy, or extracorporeal membrane oxygenation (ECMO) should not be withheld. In such cases, treatment must be provided by a multidisciplinary team, including but not limited to MFM (maternal-fetal medicine), VTE experts (including interventional radiology and vascular surgery as appropriate), and obstetric anesthesia. Lately, there has been a shift toward the creation of Pulmonary Embolism Response Teams (PERTs). Their role is to anticipate and facilitate coordination of care in cases of severe PE that necessitate the input of specialists from different fields. Those teams have been successfully utilized in cases of severe PE in pregnancy with great results.[130] Furthermore, for those with conditions that warrant treatments other than anticoagulants (ie, antithrombin concentrate) and those at increased risk for both thrombosis and bleeding (ie, concomitant von Willebrand disease or significant thrombocytopenia), involvement of thrombologists and hematologists is recommended. As suggested by Bannow et al, postpartum

patients should follow up with their primary care doctor in 1–2 weeks postpartum in order to discuss their postpartum anticoagulation plan. Nurse visits and telehealth are reasonable, but in settings where this approach is not feasible due to resource limitations, access to a reliable contact with 24-hour availability is essential.[131]

Conclusions

It is well established that the risk of VTE is higher in the peripartum period, primarily due to concomitant physiologic changes. The need to identify high-risk women, diagnose them and treat them effectively is evident, given that VTE significantly contributes to fetal and maternal mortality. VTE in pregnancy can be a diagnostic conundrum due to the physical and laboratory findings shared between normal pregnancy and systemic thrombosis. The knowledge of the accuracy of specific physical findings and symptoms and the risk each individual carries based on comorbidities and laboratory findings may help clinicians diagnose VTE promptly. As in the general population, diagnoses of DVT are made optimally by following diagnostic algorithms, including MR and CT venography, D-dimers, and serial CUS. When PE is suspected, X-ray, CTPA, V/Q scan, and possibly TTE can lead to a diagnosis or assist with decision-making. Preventing and treating PE in the obstetric population is a challenge not only because of the paucity of data regarding the safety and efficacy of anticoagulants in such patients but also because of the potential hazard that this may pose to the mother and the developing fetus. The primary anticoagulation choice in pregnancy is LMWH which should be administered for at least three months. Advanced treatments such as thrombolysis, IVC filters, and mechanical methods of thrombus removal can be associated with significant fetal morbidity and mortality but should be considered in challenging cases: failure of other treatments, massive or sub-massive PE, or acute limb-threatening DVT. Despite the radical advancements in diagnosing and treating VTE in the general population, a disproportionate amount of studies have investigated the accuracy, efficacy, and safety of the most commonly used tests and therapies in pregnant or postpartum women. A multidisciplinary approach is needed for such a high-risk and delicate population, especially for complicated cases requiring advanced treatments.

Disclosure

The authors report no conflicts of interest in this work.

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