Pregnancy and Pulmonary Embolism

Christopher Deeb Dado, MD[a], Andrew Tobias Levinson, MD, MPH[b], Ghada Bourjeily, MD[c,*]

KEYWORDS

• Pulmonary embolism • Venous thromboembolism • Pregnancy • Heparin • Multidetector CT
• Ventilation perfusion scan

KEY POINTS

- Venous thromboembolism (VTE) is responsible for 3% of all maternal deaths worldwide and 15% in the United States.
- The increased risk of VTE in pregnancy peaks immediately postpartum and may continue up to 12 weeks postpartum.
- The increased risk is attributed to the Virchow triad, inherited thrombophilias, as well as other common risk factors.
- The algorithm for diagnosing VTE differs during and immediately after pregnancy due to physiologic factors and fear of teratogenicity.
- Low molecular weight heparin and unfractionated heparin are medications of choice, as warfarin is teratogenic and novel oral anticoagulants have increased rates of bleeding and congenital anomalies.

INTRODUCTION

Venous thromboembolism (VTE) is responsible for 3% of all maternal deaths worldwide according to data from the World Health Organization.[1] Data from the developed world suggest that death rates from VTE are significantly higher, as VTE remains one of the leading causes of maternal deaths.[1,2] Recent analysis of maternal mortality in the United States showed that VTE accounted for 15% of all maternal deaths between 2003 and 2011.[3] Substandard care occurred in more than half of all deaths[4] from pulmonary embolism (PE) in the confidential enquiry into maternal deaths in the United Kingdom, highlighting the importance of understanding and overcoming challenges in the care of this condition in pregnancy. A clinician who does not treat pregnant women on a regular basis may not routinely consider many of the pregnancy-specific risk factors for VTE. Pretest probability is also quite complicated in pregnancy, as pretest probability rules have not been validated in this population, compelling the clinician to rely more heavily on imaging tests. Diagnostic procedures are also fraught with concerns about diagnostic accuracy in this population, as well as concerns for fetal safety, teratogenicity, and oncogenicity. Treatment strategies are complex, and providers need to balance efficacy while considering fetal safety, teratogenicity, pharmacodynamics, the unexpected nature of labor and delivery, and the subsequent need to weigh the risk of anticoagulation with the risk of clot

Funding: G. Bourjeily is funded by NICHD R01HL-130702 and R01HD-078515.
Conflicts of Interest: All authors have no conflicts of interest to report.
[a] Pulmonary and Critical Care Fellowship, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 593 Eddy Street, Providence, RI 02903, USA; [b] Department of Medicine, The Miriam Hospital, Warren Alpert Medical School of Brown University, 164 Summit Avenue, Providence, RI 02904, USA; [c] Department of Medicine, The Miriam Hospital, Warren Alpert Medical School of Brown University, 146 West River Street, Suite 11C, Providence, RI 02904, USA
* Corresponding author.
E-mail address: ghada_bourjeily@brown.edu

Clin Chest Med 39 (2018) 525–537
https://doi.org/10.1016/j.ccm.2018.04.007

recurrence perinatally. In this review, we examine the pregnancy-specific nuances in the risk assessment pretest probability, diagnostic evaluation, and therapeutic considerations.

Epidemiology

The risk of peripartum VTE is increased, with the postpartum period conferring a higher day-to-day risk than the antepartum period. The risk of VTE is estimated at 5 to 12 per 100,000 pregnancies antepartum compared with age-matched nonpregnant women, translating into a 0.1% absolute risk.[5,6] Although the absolute risk of VTE is lower in the postpartum period compared with the antepartum period, estimated at 0.05%,[7,8] the day-to-day risk is significantly higher when considering the significantly shorter postpartum period. The risk for VTE is highest in the first 6 weeks postpartum. Although previous data had suggested that the epidemiologic risk[9,10] and the biochemical hematological changes[11,12] that occur in pregnancy return to baseline at 6 weeks postpartum, recent claims data have shown a twofold increase in the risk of venous thrombosis (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.4–3.3) from 7 to 12 weeks postpartum compared with the same time period a year later.[13]

Pathophysiology of Thromboembolic Disease in Pregnancy

Venous stasis, vascular injury, and hypercoagulable state (Virchow triad) are all responsible for the increased risk of VTE in pregnancy. Inherited thrombophilias and other risk factors also contribute to the development of VTE in pregnancy.

Venous stasis

In pregnancy, through progesterone-induced veno-dilation,[14] renal vasodilation occurs simultaneously with systemic vasodilation and leads to 30% to 50% increase in renal blood flow and glomerular filtration rate (GFR). This rise in GFR increases distal sodium delivery, allowing for escape from the sodium-retaining effect of aldosterone. The volume expansion secondary to aldosterone increases the atrial natriuretic peptide, which in turn inhibits sodium reabsorption in the distal tubules leading to an increase in systemic volume and Na retention.[15] The increase in total body blood volume leads to an increase in blood volume in the lower extremities, from 94.7 $\pm$ 27.3 mL in nonpregnant individuals to 110.1 $\pm$ 30.2 mL in pregnancy. There is also an increase in the diameter of the common femoral vein from 10.14 $\pm$ 1.24 mm to 12.72 $\pm$ 2.27 mm, as well as proportional increases in the saphenous and popliteal vein diameters.[16] This rise in venous blood volume and pressure, along with resulting distension of the vessels, leads to stasis and increased lower extremity edema. However, it has been proposed that, unlike VTE in the general population, VTE in pregnancy may start in the pelvis[17] rather than the lower extremities, as the percentage of isolated pelvic deep venous thrombosis is significantly higher in pregnancy.[18] As the right common iliac artery crosses over the left common iliac vein, a pulsatile compression of the left-sided venous system ensues. This compression is implicated in the increase in left-sided DVTs in pregnant women, with an occurrence of 90% on the left side compared with 55% of the time in nonpregnant individuals.[19,20]

Vascular dysfunction and injury

In normal pregnancy there are circulating cytokines and growth factors that may contribute to the breakdown of the endothelial monolayer. This can lead to vascular dysfunction and injury by degrading or removing cell junctional proteins.[21] Endothelial injury also can occur during normal labor, as well as during surgical delivery.[22] In addition, the increase in blood volume and diameter of vessels causes sheer stress on the vessels, potentially leading to vascular damage.[21]

Hypercoagulable state

During pregnancy, the blood becomes hypercoagulable with increases in procoagulation factors V, VII, VIII, IX, X, and XII and von Willebrand factor. Factor VII increases up to 10-fold, whereas fibrinogen rises 2-fold.[23] Von Willebrand and factor VIII are elevated in late gestation and factor XI tends to decrease during pregnancy. There is also a decrease in anticoagulant activity with a decrease in protein S with gestational age, whereas protein C activity remains unchanged.[23] Fibrinolysis is reduced in pregnancy as a result of an enhanced activity of plasminogen activator inhibitor type I and II and a decreased activity of tissue plasminogen activator.[24]

Inherited thrombophilias

Up to 40% of women who develop VTE while pregnant are found to have an inherited thrombophilia.[19] In addition, a reported OR of 51.8 (95% CI 38.7–69.2) for thrombophilia was described in women with VTE in a study of the National Inpatient Sample evaluating risk factors for VTE.[25] Inherited thrombophilias associated with increased risk of VTE in pregnancy include factor V Leiden, Prothrombin G20210 A mutation, antithrombin deficiency, protein C deficiency, and protein S deficiency.[26] Estimates of reported thrombophilias vary in the literature and are based