

## Literature Review

## Prevention and Treatment of Venous Thromboembolism in Pregnancy

## Pencegahan dan Tatalaksana Tromboemboli Vena pada Kehamilan

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**Abstract**

**Objective:** To determine prevention and treatment of venous thromboembolism in pregnancy.

**Methods:** Literature Review.

**Results:** The diagnosis of TEV, both deep vein thrombosis (DVT) and pulmonary embolism (PE) was clinical and confirmed by imaging. D-dimers commonly used in the non-pregnant population are less useful in pregnant women. Prevention needs to be done by assessing the risk of TEV in pregnant women and giving thromboprophylaxis according to risk. Treatment of TEV in pregnant women mainly uses heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH).

**Conclusion:** The ASH recommends the use of LMWH compared with UFH for the management of acute VTE in pregnancy, in once-daily or divided doses. The recommended method of delivery for pregnant women receiving anticoagulant therapy should be planned delivery.

**Keywords:** vein thromboemboli, deep vein thrombosis, pulmonary embolism, pregnancy.

**Abstrak**

**Tujuan:** Mengetahui bagaimana pencegahan dan tatalaksana tromboemboli vena pada kehamilan.

**Metode:** Kajian Pustaka.

**Hasil:** Diagnosis TEV, baik Deep vein thrombosis (DVT) dan pulmonary embolism (PE) berdasarkan klinis dan dikonfirmasi dengan pencitraan. D-dimer yang biasa digunakan pada populasi non-hamil kurang berguna pada ibu hamil. Pencegahan perlu dilakukan dengan menilai risiko TEV pada ibu hamil dan memberikan trombofilaksis sesuai dengan risiko. Tatalaksana TEV pada ibu hamil terutama menggunakan heparin, baik unfractionated heparin (UFH) maupun low molecular weight heparin (LMWH).

**Kesimpulan:** ASH merekomendasikan penggunaan LMWH dibandingkan dengan UFH untuk pengelolaan VTE akut pada kehamilan, dalam dosis sekali sehari atau terbagi. Metode persalinan yang direkomendasikan untuk ibu hamil yang menerima terapi antikoagulan harus direncanakan persalinan.

**Kata kunci:** tromboemboli vena, deep vein thrombosis, pulmonary embolism, kehamilan.

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**INTRODUCTION**

Venous thromboembolism (VTE), especially pulmonary thromboembolism which often originates from deep vein thrombosis (DVT), is one of the most common causes of death in pregnant women. Research in America with data from 1998-2013 showed maternal mortality due to pulmonary thromboembolism is 1.5 - 1.6 deaths per 100,000 live births. The risk of death from pulmonary thromboembolism is higher in the postpartum period. A total of 8.8% of deaths in pregnancy were due to PTE in the postpartum period compared to 6.7% at the time of delivery.

In the period 2004-2014, the incidence of VTE was around 5.7 cases per 10,000 deliveries. The incidence of DVT itself decreased (5.3 to 4.4 cases per 10,000 deliveries) after the clinical community followed the guidelines and recommendations for thromboprophylaxis in pregnant women, but the incidence of pulmonary thromboembolism tends to be the same.<sup>1</sup> Approximately 15-24% of cases of DVT will develop into pulmonary thromboembolism if left unchecked.<sup>2</sup>

Pregnant women have a risk of VTE 4-4.6 times compared to women of the same age who are not pregnant. The risk of developing VTE increases with advancing gestational age, peaking at 1-3

weeks postpartum. In the 3-month postpartum period, the risk of VTE increased up to 60-fold (OR 60.1; 95% CI). This risk is increased because of vascular damage at the time of delivery.<sup>3</sup> The risk then decreases and is the same as the risk in the nonpregnant state at 12 weeks postpartum.<sup>1</sup> Risk factors that increase the incidence of VTE in the nonpregnant population also increase the risk of VTE in pregnant women, such as old age, anemia, obesity, smoking, and other factors.<sup>3</sup>

The most important factor in the incidence of VTE in pregnant women is a previous history of VTE. The incidence of VTE in pregnant women with a history of VTE and who were not given thromboprophylaxis was found to be very high, around 1000 cases per 10,000 pregnant women (10%). The second important factor in VTE in pregnant women is hereditary thrombophilia. The risk of VTE in pregnant women with thrombophilia is much higher than in pregnant women in general (OR 15.4, 95% CI).<sup>3</sup> History of cardiovascular disease is the third highest risk factor with an incidence of 100-200 cases per 10,000 pregnant women. Preeclampsia, one of the most common complications of pregnancy, also increases the risk of VTE. The study of Kane et al. showed that preeclampsia increased the risk of VTE in the postpartum period by 1.6 times, but not in the prenatal/antepartum period.<sup>4</sup> Another risk factor that significantly increases the risk of VTE in pregnant women is a cesarean section, but this risk was found to decrease with thromboprophylaxis according to recent guidelines.<sup>3</sup>

The increased risk of VTE in pregnant women, especially those accompanied by other risk factors and the high morbidity and mortality of VTE, requires early diagnosis, prevention, and appropriate management. The purpose of this review is to discuss the diagnosis, prevention, and management of thromboembolism in pregnancy.

**Table 1.** Risk factors for venous thromboembolism in pregnancy <sup>1,3,4</sup>

#### Risk Factors

Previous VTE history
Hereditary hemophilia
History of cardiovascular disease
Post-partum
Pre-eclampsia
Elderly
Anemia
Obesity
Smoking

## METHODS

The method in this research is to use literature review from various references.

## RESULTS

### PATHOGENESIS OF THROMBOEMBOLISM IN PREGNANCY

Pregnancy and the postpartum period are prothrombotic conditions characterized by an increase in the three components of Virchow's triad, namely venous stasis, endothelial damage, and hypercoagulation. Venous stasis in the lower extremities occurs in pregnancy due to progesterone-induced venous-vasodilation and compression of the large veins by the gravid uterus. Although blood volume and venous return are increased, the linear velocity of the lower extremity veins is reduced because of increased venous capacity. This venous stasis lasts up to about 6 weeks postpartum.<sup>5</sup>

Endothelial damage that occurs during labor on the uteroplacental surface may increase the risk of VTE in the postpartum period. The use of assistive devices such as forceps, vacuum, or surgery can exacerbate these risks. The increased blood volume in pregnancy may also cause shear stress on the blood vessels.<sup>6</sup>

Pregnancy is a hypercoagulable condition characterized by an increase in pro coagulation factors such as factors V, VII, VIII, IX, X, XII, and von Willebrand factor. This condition is also accompanied by reduced anticoagulation factors, namely protein S. Fibrinolysis is also reduced due to increased activity of plasminogen activator inhibitor types I and II, and reduced activity of tissue plasminogen activator.<sup>6</sup> These changes are physiological to prepare for blood clotting during labor, which is characterized by an increase in D-dimer and prothrombin fragments.

### DIAGNOSIS OF VTE IN PREGNANCY

#### Deep vein thrombosis (DVT)

The most common complaint in more than 80% of pregnant women with DVT is pain and swelling in the extremities. However, this complaint is also often complained by pregnant women without DVT. A unilateral calf circumference difference of more than 2 cm is a sign suggestive of lower extremity DVT. In the guidelines of the American College of Obstetricians and Gynecologists

(ACOG), the initial investigation recommended in patients presenting with suspected DVT is compression ultrasonography (CUS). Thromboembolism in pregnant patients is usually found in the iliofemoral or ileal, in contrast to the general population, which is usually found in the distal.

When CUS results are negative or doubtful and iliac vein thrombosis is suspected (swelling of the whole leg with or without back, waist, or buttocks pain), the next investigation recommended is iliac vein Doppler ultrasonography, venography, or magnetic resonance imaging (MRI). Empirical anticoagulation may also be given in some cases. When the results are negative and there is no suspicion of iliac vein thrombosis, re-examination can be performed on day 3 and day 7.<sup>7</sup>

The D-dimer examination is less useful in ruling out VTE in pregnant women because normal pregnancy is accompanied by a progressive increase in D-dimer, so it is not recommended.<sup>7</sup> The use of a scoring system such as the Wells score needs to be interpreted with caution as this score was not validated for the pregnant maternal population.<sup>8</sup> The use of clinical prediction LEfT (Left leg, Edema [calf diameter difference 2cm], First trimester) can help in predicting DVT in pregnant women. In a study of 194 pregnant women, DVT was not found in patients with a score of 0. However, this system should not be used as the sole means of excluding DVT. This tool also still needs further validation.<sup>9</sup>

#### *Pulmonary Embolism / PE*

PE symptoms such as dyspnea, palpitations, chest pain that is aggravated by movement are often found in pregnant women with non-thrombotic causes, such as gastroesophageal reflux or discomfort due to an enlarged uterus. This causes the diagnosis of PE in pregnant women to be difficult.<sup>8</sup> In addition, scoring systems such as Wells or Geneva are not validated for pregnant patients. Clinicians need to consider the diagnosis of PE in pregnant women who present with these symptoms given the high mortality. Symptoms that can be found in PE include palpitations, anxiety, pleuritic chest pain, cyanosis, and cough with or without hemoptoe. On physical examination, usually found tachypnea, crackles, decreased breath sounds, and tachycardia. In some cases, signs of right ventricular failure can also be found, such as a split-second heart sound, jugular venous distension, parasternal removal, and hepatomegaly.<sup>2</sup>

Investigations such as blood gas analysis (BGA) are neither sensitive nor specific for the diagnosis of PE. Patients with PE usually develop a respiratory alkalosis, similar to that found in normal pregnancy. Normal PO<sub>2</sub> and PCO<sub>2</sub> levels are often found in patients with PE, so normal BGA levels cannot rule out PE.<sup>10</sup> Examination of D-dimer, such as in DVT is difficult to do because there is no normal value of D-dimer in pregnant women.<sup>11</sup>

According to ACOG guidelines, ventilation-perfusion scanning (V/Q scanning) and computed tomographic pulmonary angiography (CTPA) examinations can be performed in pregnant women with suspected PE. Clinical practice guidelines from the American Thoracic Society recommend a chest X-ray in all pregnant patients with suspected PE without DVT symptoms. If the photo is abnormal, it is recommended to continue with CTPA examination, while the normal photo is followed by V/Q scanning.<sup>12</sup>

### **PREVENTION OF THROMBOEMBOLISM IN PREGNANCY**

Not all pregnant or postpartum women require thromboprophylaxis. ACOG recommends assessing VTE risk factors for all pregnant women before or in early pregnancy.<sup>7</sup> One tool that can be used to assess this risk is to use the modified Padua or Caprini scoring system for the pregnant woman population. ACOG also recommends the assessment of thrombophilia in pregnant women with a previous history of VTE.<sup>13</sup>

#### *Thromboprophylaxis in Cesarean Section*

In cesarean delivery, ACOG and the American College of Chest Physician (ACCP) recommend using pneumatic compression devices and early mobilization for all pregnant women who are not receiving pharmacological thromboprophylaxis.<sup>13</sup> In pregnant women at high risk of VTE, the recommendations are not clear. ACOG recommends a combination of pneumatic compression and low molecular weight heparin (LMWH).<sup>7</sup> ACCP recommends combination thromboprophylaxis for patients with a score of 5 or more. In pregnancy, this score is usually found in patients with a history of VTE or a family history or with thrombophilia.<sup>13</sup>

#### *Antepartum and Postpartum Thromboprophylaxis*

Pharmacological thromboprophylaxis can be given to pregnant women with a high risk of

VTE. The recommendations from ACOG 2018 regarding pregnant women who are indicated for pharmacological thromboprophylaxis can be seen in Table 2. These recommendations

consider the advantages of preventing VTE and the disadvantages of fetal complications and bleeding.<sup>7</sup>

**Table 2.** Pharmacological thromboprophylaxis recommendations in pregnancy and the puerperium <sup>7</sup>

Clinical Scenario	Antepartum Management	Postpartum Management
No history of VTE or thrombophilia	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
VTE diagnosed during pregnancy	LMWH/UFH therapeutic dose	LMWH/UFH therapeutic dose at least 6 weeks postpartum. The duration of administration may be longer. Oral anticoagulants may be considered.
History of one episode of VTE precipitated by causes other than estrogen or pregnancy (surgery, trauma, immobilization), without thrombophilia	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
History of one unprovoked VTE episode, including pregnancy-related or hormonal contraceptives	LMWH/UFH moderate prophylactic dose or therapeutic dose	LMWH/UFH prophylactic dose, moderate dose, or therapeutic dose for 6 weeks postpartum
Low-risk thrombophilia** with no history of VTE	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
Low-risk thrombophilia with a nuclear family history of VTE	Surveillance or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or moderate dose LMWH/UFH
High-risk thrombophilia*** no history of VTE	Prophylactic or moderate dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or moderate dose LMWH/UFH
High-risk thrombophilia with a history of one episode of VTE/ nuclear family history	LMWH/UFH prophylactic dose, moderate dose, or therapeutic dose	Prophylactic postpartum anticoagulation therapy or moderate/therapeutic doses of LMWH/UFH for 6 weeks (level of therapy should be similar to antepartum management)
History of two or more VTE episodes	Moderate/therapeutic dose LMWH/UFH	Postpartum anticoagulation therapy with moderate/therapeutic doses of LMWH/UFH for 6 weeks (level of therapy should be similar to antepartum management)
History of two or more VTE episodes – being on long-term anticoagulant medication	LMWH/UFH therapeutic dose	Continue long-term anticoagulant therapy.

\*Obesity, prolonged immobilization, cesarean delivery, family history of VTE

\*\* Low-risk thrombophilia: Factor V Leiden heterozygous; heterozygous G20210A prothrombin gene mutation; protein C or protein S deficiency; antiphospholipid antibodies.

\*\*\* High-risk thrombophilia: Homozygous Factor V Leiden; homozygous G20210A prothrombin gene mutation; Heterozygous Factor V Leiden plus heterozygous G20210A prothrombin gene mutation; antithrombin deficiency.

## MANAGEMENT OF THROMBOEMBOLISM IN PREGNANCY

Initial VTE management in pregnant women depends on the degree of suspicion of PE. In cases with a strong suspicion of PE, empiric anticoagulation is given until there is no evidence of VTE. In patients with suspected PE but who have contraindications to anticoagulation, a diagnostic evaluation is preceded by administration of therapy without anticoagulation (eg inferior vena cava filter) after VTE is confirmed.

When anticoagulation is indicated, the recommended initiation of anticoagulation by both ACCP and ACOG is subcutaneous therapeutic dose LMWH.<sup>7,14</sup> LMWH is preferable to intravenous (IV) Unfractionated Heparin (UFH) because it has a better efficacy and safety profile. These findings were obtained by extrapolating a meta-analysis from 22 randomized clinical trials with the general (nonpregnant) population. The use of subcutaneous LMWH has a lower mortality rate, lower recurrent thrombosis, and lower heavy bleeding compared to IV UFH.<sup>15</sup> In patients with PE or situations requiring immediate delivery, surgery, or thrombolysis, IV UFH is preferred because it has a shorter half-life and can be discontinued protamine when necessary. Oral anticoagulants are avoided in pregnancy because of the unknown safety profile. The use of warfarin is avoided because it is teratogenic, especially in the first trimester.<sup>7</sup>

In patients who are about to give birth, the administration of LMWH should be discontinued at least 12 hours before induction. Discontinuation for 24 hours is recommended for the use of therapeutic doses. In the use of heparin 7500 U SC twice daily or more, discontinuation should be carried out for 12 hours with an evaluation of coagulation status. This discontinuation is done to avoid spinal hematoma in the administration of neuraxial anesthesia.<sup>7</sup>

After delivery, the heparin regimen should be restarted after 12 hours of cesarean section or 6 hours after vaginal delivery, unless significant bleeding occurs. For LMWH administration,

the consensus of the Society for Obstetric Anesthesia and Perinatology recommends delaying reinitiation for at least 24 hours or using IV UFH if earlier initiation is desired.<sup>16</sup> In patients requiring anticoagulation for longer than 6 weeks, bridging to warfarin or direct oral anticoagulation (if not breastfeeding) may be considered. The initial dose of warfarin is 5 mg once daily, with subsequent doses determined by the international normalized ratio (INR).<sup>7</sup>

### Thrombolysis / Thrombectomy

Thrombolytic agents are known to have side effects, namely severe maternal bleeding, so they are only given to life-threatening acute PE. Thrombectomy can be performed to save lives if other attempts fail. Thrombectomy is a procedure in which an intravenous catheter is inserted to reach the thrombus, then placing a thrombolytic agent around the thrombus in the hope that the thrombus will lysis. In a literature review, Catheter Directed Thrombolysis (CDT) had a lower risk of bleeding but the possibility of systemic spread of the thrombolytic agent was possible.<sup>17</sup>

## ANTICOAGULANT REGIMEN IN PREGNANCY

The use of anticoagulants in pregnant women is different from the general population. The benefits and risks need to be considered for both the fetus and the mother. Heparin is the recommended anticoagulant in pregnancy. The pharmacokinetics of heparin will change in pregnancy as the total blood volume and glomerular filtration rate increase. This causes heparin to have a lower half-life and peak plasma concentration, so larger doses are required. The therapeutic dose of heparin was adjusted according to the activated partial thromboplastin time (aPTT), while the LMWH was adjusted according to the mother's weight. At prophylactic doses or moderate doses, the dose given is specific according to the type of drug given. The American Society of Hematology (ASH) recommends the use of LMWH over the use of UFH in the management of acute VTE, with the LMWH dose being once or divided into twice-daily doses.<sup>18</sup> For pregnant women receiving anticoagulant therapy, the ASH recommends scheduled delivery, with stopping anticoagulation a few days before delivery.<sup>18</sup> Management of acute VTE in the anticoagulant regimen taken from the ACOG practical bulletin can be seen in Table 3.<sup>7</sup>

**Table 3.** Anticoagulant regimen <sup>7</sup>

Anticoagulant regimen	Dose
Prophylactic LMWH	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 U SC once daily Tinzaparin, 4,500 U SC once daily Nadroparin, 2850 U SC once daily
LMWH moderate dose	Enoxaparin, 40 mg SC every 12 hours Dalteparin, 5,000 U SC every 12 hours
LMWH therapeutic dose	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 U/kg once daily Tinzaparin, 175 U/kg once daily Dalteparin, 100U/kg every 12 hours Anti-Xa targets in a therapeutic range of 0.6-1.0U/ml 4 hours after injection at twice-daily doses; dose increase may be required for daily dosing.
Prophylactic UFH	UFH 5,000-7,000 U SC every 12 hours in the first trimester UFH 7,500-10,000 U SC every 12 hours in the second trimester UFH 10,000 U SC every 12 hours in the third trimester, unless the aPTT is elevated
UFH therapeutic dose	UFH 10,000 U or more SC every 12 hours with dose adjusted to aPTT in the therapeutic range (1.5-2.5x control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, moderate, or therapeutic doses of LMWH for 6-8 weeks as indicated. Oral anticoagulation may be considered according to the duration of therapy, lactation, and patient preferences

## CONCLUSIONS AND SUGGESTIONS

VTE risk assessment in all pregnant women needs to be done at the first antenatal visit or before pregnancy. Further assessment of thrombophilia needs to be carried out in pregnant women with a previous history of VTE. Thromboprophylaxis with heparin is indicated in patients at high risk of VTE, eg those with a history of high-risk thrombophilia and a history of recurrent VTE. The ASH recommends the use of LMWH compared with UFH for the management of acute VTE in pregnancy, in once-daily or divided doses. The recommended method of delivery for pregnant women receiving anticoagulant therapy should be planned delivery.

## REFERENCES

- Abe K, Kuklina EV, Hooper WC, Callaghan WM. Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States. *Semin Perinatol.* 2019;43(4):200–4.
- Agnesha F, Rahardjo S. Tromboemboli pada kehamilan. *Jurnal Komplikasi Anestesi.* 2018;5:11.
- Parunov LA, Soshitova NP, Ovanesov MV, Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (TEV) associated with pregnancy. *Birth Defects Res C Embryo Today.* 2015;105(3):167–84.
- Kane EV, Calderwood C, Dobbie R, Morris C, Roman E, Greer IA. A population-based study of venous thrombosis in pregnancy in Scotland 1980-2005. *Eur J Obstet Gynecol Reprod Biol.* 2013;169(2):223–9.
- Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. *Cardiovasc Diagn Ther.* 2017;7(Suppl 3):S309–19.
- Dado CD, Levinson AT, Bourjeily G. Pregnancy and Pulmonary Embolism. *Clin Chest Med.* 2018;39(3):525–37.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. *Obstet Gynecol.* 2018;132(1):e1–17.
- Chan W-S. Diagnosis of venous thromboembolism in pregnancy. *Thromb Res.* 2018;163:221–8.
- Chan W-S, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med.* 2009;151(2):85–92.
- Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest.* 1996;109(1):78–81.
- Damodaram M, Kaladindi M, Luckit J, Yoong W. D-dimers as a screening test for venous thromboembolism in pregnancy: is it of any use? *J Obstet Gynaecol.* 2009;29(2):101–3.

12. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boisselle PM, Hurwitz LM, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. *Am J Respir Crit Care Med*. 2011;184(10):1200–8.
13. Alton ME, Friedman AM, Smiley RM, Montgomery DM, Paidas MJ, Oria R, et al. National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism. *Obstet Gynecol*. 2016;128(4):688–98.
14. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. TEV, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST*. 2012;141(2):e691S–e736S.
15. Middeldorp S. How I treat pregnancy-related venous thromboembolism. *Blood*. 2011;118(20):5394–400.
16. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants. *Anesth Analg*. 2018;126(3):928–44.
17. Maurizka AD. Catheter directed thrombolysis terapi emboli paru pada ibu hamil. *Wellness And Healthy Magazine*. 2020;2(1):41–8.
18. Shannon M. Bates, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism : venous thromboembolism in the context of pregnancy. 2018;2(22) : 3317-3358.