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Prevention and Treatment of Venous Thromboembolism in Pregnancy

Indones J Obstet Gynecol

I12 Suparman

Literature Review

Prevention and Treatment of Venous Thromboembolism in Pregnancy
Pencegahan dan Tatalaksana Tromboemboli Vena pada Kehamilan

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Faculty of Medicine Sam Ratulangi University
Prof. Dr. R. D. Kandou General Hospital
Manado, North Celebes

Abstract
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Pencegahan dan Tatalaksana Tromboemboli Vena pada Kehamilan

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Manado, North Celebes

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 thrombophylaxis 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.

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. Approximately 15-24% of cases of DVT will develop into pulmonary thromboembolism if left unchecked.2

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. The risk then decreases and is the same as the risk in the nonpregnant state at 12 weeks postpartum. 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.

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). 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. 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.

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

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE history</td>
</tr>
<tr>
<td>Hereditary hemophilia</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
</tr>
<tr>
<td>Post-partum</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Elderly</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
</tbody>
</table>

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.

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.

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. 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...
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 PO2 and PCO2 levels are often found in patients with PE, so normal BGA levels cannot rule out PE. Examination of D-dimer, such as in DVT is difficult to do because there is no normal value of D-dimer in pregnant women.

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.

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. 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.

Thrombophylaxis 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. 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). 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.

Antepartum and Postpartum Thrombophylaxis

Pharmacological thromboprophylaxis can be given to pregnant women with a high risk of...
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.7

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

Table 2: Pharmacological thromboprophylaxis recommendations in pregnancy and the puerperium7
**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 (e.g., 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. 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. 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.

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.

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. 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).

**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.

**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. For pregnant women receiving anticoagulant therapy, the ASH recommends scheduled delivery, with stopping anticoagulation a few days before delivery.

Management of acute VTE in the anticoagulant regimen taken from the ACOG practical bulletin can be seen in Table 3.
Table 3. Anticoagulant regimen

<table>
<thead>
<tr>
<th>Anticoagulant regimen</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic LMWH</td>
<td>Enoxaparin, 40 mg SC once daily</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 5,000 U SC once daily</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin, 4,500 U SC once daily</td>
</tr>
<tr>
<td></td>
<td>Nadroparin, 2,850 U SC once daily</td>
</tr>
<tr>
<td>LMWH moderate dose</td>
<td>Enoxaparin, 40 mg SC every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 5,000 U SC every 12 hours</td>
</tr>
<tr>
<td>LMWH therapeutic dose</td>
<td>Enoxaparin, 1 mg/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 200 U/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin, 175 U/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dalteparin, 100 U/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Anti-Xa targets in a therapeutic range of 0.6–1.0U/ml 4 hours after</td>
</tr>
<tr>
<td></td>
<td>injection at twice-daily doses; dose increase may be required for</td>
</tr>
<tr>
<td></td>
<td>daily dosing.</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>UFH 5,000–7,000 U SC every 12 hours in the first trimester</td>
</tr>
<tr>
<td></td>
<td>UFH 7,500–10,000 U SC every 12 hours in the second trimester</td>
</tr>
<tr>
<td></td>
<td>UFH 10,000 U SC every 12 hours in the third trimester, unless the</td>
</tr>
<tr>
<td></td>
<td>aPTT is elevated</td>
</tr>
<tr>
<td>UFH therapeutic dose</td>
<td>UFH 10,000 U or more SC every 12 hours with dose adjusted to</td>
</tr>
<tr>
<td></td>
<td>aPTT in the therapeutic range (1.5–2.5x control) 6 hours after</td>
</tr>
<tr>
<td></td>
<td>injection</td>
</tr>
<tr>
<td>Postpartum anticoagulation</td>
<td>Prophylactic, moderate, or therapeutic doses of LMWH for 6–8 weeks</td>
</tr>
<tr>
<td></td>
<td>as indicated. Oral anticoagulation may be considered</td>
</tr>
<tr>
<td></td>
<td>according to the duration of therapy, lactation, and patient</td>
</tr>
<tr>
<td></td>
<td>preferences</td>
</tr>
</tbody>
</table>

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


