Anticoagulants in Pregnancy

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عشق سوزان است بسم اللّه الرحمن الرحيم

هرکه خواهان است بسم اللّه الرحمن الرحيم
ای لبانت محیی الاموات لبخندی بزن
مردن آسان است بسم الله الرحمن الرحیم

میزبان عشق است و وای از عشق! غوغا می‌کند
هر که مهمان است بسم الله الرحمن الرحیم
• pregnancy is associated with a 5-fold increase in the risk of venous thromboembolism (VTE), with the risk rising to 20-fold or more during puerperium.
• The risk further increases if an underlying thrombophilia is present.
• The risk of VTE persists until nearly 12 weeks postpartum
Indications for antithrombotic agents
Indications for antithrombotic agents

- acute VTE and valvular heart disease,
- as well as for the prevention of pregnancy-related complications in women with antithrombin deficiency
- antiphospholipid antibody (APLA) syndrome.
- other thrombophilias who have had a prior VTE.
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

- Normal pregnancy is associated with a hypercoagulable state, which arises from the following:

- Increased serum levels of procoagulants: Including fibrinogen and factors II, VII, VIII, X, and XII
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

• Normal pregnancy is associated with a hypercoagulable state, which arises from the following:

  • Decreased protein S levels
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

• Normal pregnancy is associated with a hypercoagulable state, which arises from the following:

• Increased resistance to activated protein C: Observed in the second and third trimesters of pregnancy
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

• Normal pregnancy is associated with a hypercoagulable state, which arises from the following:

• Increased serum plasminogen activator inhibitor-1 (PAI-1) and placental PAI-2 levels: Lead to a decreased fibrinolytic state
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

• Normal pregnancy is associated with a hypercoagulable state, which arises from the following:

• Venous stasis: Resulting from pressure of the gravid uterus on the inferior vena cava and decreased venous tone
Etiology of thrombosis in pregnancy
Etiology of thrombosis in pregnancy

• The risk of pregnancy-related VTE is particularly high in heterozygous carriers of factor V Leiden (4-fold to 16-fold increase)
• the prothrombin mutation (15-fold increase),
• as well as in women with APLAs (5% incidence)
Anticoagulation in pregnant patients with valvular heart disease

- Warfarin is more efficacious than unfractionated heparin (UFH) for thromboembolic prophylaxis of pregnant women with mechanical valves
Anticoagulation in pregnant patients with valvular heart disease

- Unfortunately, warfarin therapy in the first trimester of pregnancy is associated with a substantial increase in fetal anomalies,
• Complications secondary to anticoagulation during pregnancy
Fetal complications
Fetal complications

- Warfarin crosses the placenta and can cause fetal bleeding and teratogenicity, with the latter occurring mainly during the first trimester.
- Neither UFH nor low-molecular weight heparin (LMWH) cross the placenta; therefore, these agents do not cause fetal bleeding or teratogenicity,
- although bleeding at the utero-placental junction and fetal wastage are possible.
Maternal complications
Maternal complications

- Major bleeding in patients treated with UFH therapy (2%)

- Heparin-induced thrombocytopenia (3%)

- Vertebral fracture from heparin-induced osteoporosis (2-3%)

- Significant reduction in bone density from long-term UFH therapy (about 30%);
  - LMWH causes less osteoporosis, including less heparin-induced osteoporosis, than does UFH.
Overview

• The use of anticoagulants and thrombolytics in pregnancy is an important consideration, because pregnancy is associated with a 4-fold increase in the risk of venous thromboembolism (VTE), with the risk rising to 14-fold during puerperium. The risk further increases if an underlying thrombophilia is present.
Anticoagulants
Anticoagulants

• Warfarin is an oral anticoagulant that interferes with the liver's synthesis of vitamin K–dependent clotting factors, which leads to the depletion of factors II (prothrombin), VII, IX, and X and to the prolongation of clotting times (ie, international normalized ratio [INR]).
Anticoagulants
Anticoagulants

- **Rivaroxaban** is an orally active factor Xa inhibitor that prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT).

- **Dabigatran** is an orally administered direct thrombin inhibitor that also results in prolongation of the aPTT.

- Unlike warfarin, the pharmacokinetics of **rivaroxaban** and **dabigatran** are predictable; thus, **routine monitoring of coagulation parameters is not required when one of these agents is used**. However, warfarin has been used extensively in pregnancy, while the safety and efficacy of **rivaroxaban** or **dabigatran** in pregnancy have not been established.
Anticoagulants

- The most commonly used parenteral anticoagulants inactivate thrombin and/or factor Xa without depleting circulating levels of clotting factors.
Anticoagulants
Anticoagulants

- Unfractionated heparin (UFH),
- Low–molecular weight heparin (LMWH),
- Heparinoids,
- Synthetic pentasaccharide inhibitors (e.g., fondaparinux),
- Direct thrombin inhibitors (i.e., hirudin and argatroban) belong to this category.

- LMWH is preferred over UFH for the prevention and treatment of VTE owing to its ease of use, as well as its greater efficacy and safety profile.
Indications for Antithrombotic Agents

- Acute and chronic VTE (including pulmonary embolism)

- Atrial fibrillation

- Valvular and structural heart disease

- Ischemic stroke

- Acute coronary syndromes

- Peripheral artery occlusive disease
Indications in pregnancy
Indications in pregnancy

- acute VTE and valvular heart disease,
- as well as for the prevention of pregnancy-related complications in women with antithrombin deficiency,
- antiphospholipid antibody (APLA) syndrome,
- or other thrombophilias,
Etiology of Thrombosis in Pregnancy
VTE and DVT

• Normal pregnancy is associated with a hypercoagulable state, which is at least partly due to increased serum levels of procoagulants, such as fibrinogen and factors II, VII, VIII, X, and XII. In addition, protein S levels decrease during pregnancy.

• Increased resistance to activated protein C is observed in the second and third trimesters of pregnancy.
VTE and DVT

• Concomitantly, serum plasminogen activator inhibitor-1 (PAI-1) and placental PAI-2 increase with pregnancy, which leads to a decreased fibrinolytic state.

• Venous stasis resulting from pressure of the gravid uterus on the inferior vena cava and decreased venous tone are additional predisposing factors for VTE.
Risk VTE, DVT
VTE and DVT

- The risk of pregnancy-related VTE is particularly high in heterozygous carriers of factor V Leiden (4-fold to 16-fold increase).
- the prothrombin mutation (15-fold increase).
- in women with APLAs (5% incidence.).
VTE and DVT

• In approximately 85% of cases, DVT of the lower extremity occurs on the left side during pregnancy.
Prevention and Treatment of Venous Thromboembolism

The American College of Chest Physicians (ACCP).
Pregnant women

VTE
Pregnant women

- LMWH instead of unfractionated heparin (UFH), to prevent and treat VTE
Women who become pregnant while receiving anticoagulant therapy for VTE

بیمار دوم خانم حامله که داروی انتی‌گواگولان برای دریافت VTE می‌کند؟
• LMWH instead of vitamin K antagonists during the first trimester.
• and during the second and third trimesters
• as well as during late pregnancy when birth is imminent
• بیمار سوم خانم که قصد بارداری دارد و مصرف طولانی وارفارین دارد، کاندید درمانی LMWH می‌باشد؟
• Frequent pregnancy tests and the substitution of LMWH for vitamin K when the patient becomes pregnant
Pregnant women

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• Restrict fondaparinux and parenteral direct thrombin inhibitors to patients who not only have severe allergic reactions to heparin but who also cannot take danaparoid
Pregnant women
• No oral direct thrombin (eg, dabigatran)

• NO anti-Xa (eg, rivaroxaban, apixaban) inhibitors
Pregnant women on long-term vitamin K antagonists
• Adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy, with long-term anticoagulants resumed postpartum
Pregnant women who are homozygous for factor V Leiden or the prothrombin 20210A mutation, who have a family history of VTE but no history of it themselves
• Antepartum: Prophylaxis with prophylactic- or intermediate-dose LMWH

• Postpartum: 6 weeks of prophylaxis with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted to achieve an INR of 2.0 to 3.0
Pregnant women with all other thrombophilias, who have a family history of VTE but no history of it themselves
• Antepartum: Clinical vigilance

• Postpartum: Prophylaxis with prophylactic- or intermediate-dose LMWH or, in women with no protein C or S deficiency, vitamin K antagonists targeted to achieve an INR of 2.0 to 3.0 (grade 2C)
• Pregnant women who are homozygous for factor V Leiden or the prothrombin 20210A mutation but with no personal or family history of VTE
• Antepartum: Clinical vigilance

• Postpartum: Six weeks of prophylaxis with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted to achieve an INR of 2.0 to 3.0 (grade 2B)
• Women who have had 3 or more miscarriages prior to 10 weeks' gestation
• Screening for antiphospholipid antibodies (APLAs)
بیمار هفتم

• Women who match the laboratory criteria for APLA syndrome and, based on a history of 3 or more pregnancy losses, fulfill the clinical APLA criteria
• Antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with 75-100 mg/day of low-dose aspirin
• Women with inherited thrombophilia and a history of pregnancy complications
• No antithrombotic prophylaxis
بیمار نهم

• Women at risk for preeclampsia
• Low-dose aspirin beginning the second trimester and continuing for the rest of the pregnancy)
• Women without APLA or thrombophilia but who have had 2 or more miscarriages
• No antithrombotic prophylaxis
Pregnant women with mechanical heart valves
One of the following anticoagulant regimens

- (a) Adjusted-dose LMWH twice a day throughout pregnancy
One of the following anticoagulant regimens (all of which are grade

- (b) Adjusted-dose UFH throughout pregnancy, with subcutaneous administration every 12 hours; adjust doses to keep the midinterval activated partial thromboplastin time (aPTT) at least twice control or reach an anti-Xa heparin level of 0.35-0.70 units/mL
One of the following anticoagulant regimens (all of which are grade

• (c) Administer UFH or LMWH as detailed above until the 13th week, with vitamin K antagonists then substituted for heparin and with UFH or LMWH administration resumed close to delivery
Women considered to have a very high risk of thromboembolism in whom the efficacy and safety of UFH or LMWH in the above-detailed doses are a matter of concern (eg, women with an older-generation prosthesis in the mitral position or who have a history of thromboembolism)
• Vitamin K antagonists administered throughout the pregnancy but replaced with UFH or LMWH close to delivery (grade 2C)
نکات مهم

• Pregnant women with prosthetic valves and a high thromboembolic risk
• Addition of 75-100 mg/day of low-dose aspirin
نکات مهم

Prosthetic heart valves and anticoagulation
Prosthetic heart valves and anticoagulation

• Anticoagulation is recommended in most pregnant patients with a mechanical prosthetic heart valve (but is not required in those with a bioprosthetic valve). However, patients with a mechanical prosthetic valve who require anticoagulation are exposed to special risks during pregnancy. Therefore, whenever possible, symptomatic or severe valvular lesions should be addressed before conception.
• Warfarin is more efficacious than UFH for thromboembolic prophylaxis of pregnant women with mechanical valves.

• Unfortunately, warfarin therapy in the first trimester of pregnancy is associated with a substantial increase in fetal anomalies, and anticoagulation with any agent is associated with an increased incidence of fetal wastage (approximately 30%), prematurity (approximately 45%), and low birth weight (approximately 50%).
Fetal complications of anticoagulants during pregnancy
Fetal complications of anticoagulants during pregnancy

• Warfarin crosses the placenta and can cause fetal bleeding and teratogenicity, with the latter occurring mainly during the first trimester

• Neither UFH nor LMWH cross the placenta; therefore, these agents do not cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction and fetal wastage are possible.
Maternal complications of anticoagulants during pregnancy
Maternal complications of anticoagulants during pregnancy

• The rate of major bleeding in patients treated with UFH therapy is 2%.[

• Approximately 3% of patients receiving UFH develop immune thrombocytopenia (so-called heparin-induced thrombocytopenia [HIT]), which predisposes them to venous and arterial thrombosis.

• Heparin-induced osteoporosis causes vertebral fracture in 2-3% of patients, and significant reduction in bone density is seen in about 30% of patients receiving long-term UFH.

• LMWH causes less osteoporosis and HIT than UFH.
خدا نگه دار