Thrombophilia and recurrent miscarriages

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Abstract

Hereditary and acquired thrombophilia are associated with recurrent miscarriages. Anti-thrombotic therapy can re-establish the haemostatic balance and improve the prognosis during pregnancy.

In this article, the authors give an introduction to thrombophilia associated with obstetric complications, including some therapeutic and prophylactic aspects of thromboembolic events during pregnancy.

Key words: Venous thromboembolism, low molecular weight heparin, thrombophilia.

INTRODUCTION

In the last century, Virchow described the mechanisms underlying thrombosis, emphasizing lesions of the vascular wall, states of venous stasis and changes in blood composition, known as hypercoagulable states. Thus, the concept of thrombophilia arises, consisting of a set of disorders characterized by the fact that they promote changes in blood coagulation, which determine a higher risk of thrombosis.

Venous thromboembolism is a major cause of obstetric morbidity and mortality, but the actual incidence of deep vein thrombosis (DVT) during pregnancy and postpartum has not yet been completely established.[1] In general, we can state that there is a six to ten times higher risk of the occurrence of venous thromboembolism (VTE) during pregnancy, and that DVT occurs in 1 to 2 cases per 1000 gestations.

Traditionally, the risk of thrombosis during pregnancy is higher during the third trimester of gestation and, particularly, during the puerperium period (six weeks after delivery).[1, 2]

Several factors may be associated with and contribute to the occurrence of VTE during pregnancy. Venous stasis, either by increased venous distensibility and capacitance, demonstrable in the first trimester (with a consequent reduction of venous flow velocity in the lower limbs), or by compression of the inferior vena cava and left iliac vein by the uterus, is likely to be the main pathophysiological mechanism. Increased levels of fibrinogen and other coagulation factors, particularly factors II, VII and X, and reduced levels of their natural inhibitors (antithrombin III, protein C and S), as well as reduced fibrinolytic activity during pregnancy, produce a relative hypercoagulable state.[2]

Trauma to the pelvic veins during vaginal delivery, and tissue damage during caesarean section, may contribute to immediate venous thrombosis during puerperium.[2, 3]

The following risk factors are believed to be associated with the development of DVT during pregnancy: a history of VTE or superficial phlebitis, age over 30, obesity, prolonged bedrest, inherited thrombophilia, multiparity and caesarean section, among others *(Table I)*. It is important to point out that about 50% of pregnant women who have an episode of DVT of the lower limbs, associated with personal and family history of thrombosis, also have thrombophilia.[3,4]

Embryo-foetal losses (within less than three weeks of gestation) are classified into two types according to the time they occur:

1) clinical abortion, defined as the termination of pregnancy when the embryo sac can be seen in the ultrasound (five to six weeks of amenorrhoea) and

2) preclinical abortion or early loss of pregnancy, defined as positive pregnancy test without ultrasound imaging of the embryo sac.[4]

Early pregnancy losses are often under-diagnosed, since these are gestations that terminate very early, before the missed menstrual period, and so they usually pass unnoticed.[4]

Early, recurrent spontaneous abortion, defined as

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TABLE I

Risk factors for VTE during pregnancy and puerperium

Pre-existing	Recurrent or transient
Previous VTE	Surgical procedures in pregnancy and puerperium (curettage)
Inherited thrombophilia	Dehydration
AT III deficiency	Ovarian hyperstimulation syndrome
Protein C deficiency	Severe infection
Protein S deficiency	Pyelonephritis,
Factor V Leiden	Immobilization (> 4 days bedrest)
Prothrombin gene mutation	Pre-eclampsia
Acquired APLS, lupus anticoagulant, anti-cardiolipin antibodies	Excessive blood loss
Age > 35 years	Long travels
Obesity (BMI > 30 kg/m2) during preconception and early pregnancy	Prolonged labor
Childbirth > 4	Midcavity instrumental delivery
Large varicose veins	Postpartum immobility
Paraplegia	
Sickle cell disease	
Inflammatory diseases (inflammatory bowel disease)	
Some medical diseases (nephritic syndrome, heart diseases)	
Myeloproliferative diseases	
Polycythemia Vera	

two or more consecutive embryo-foetal losses, affects about 2%-3% of women of childbearing age. Its etiology includes genetic, anatomical, microbiological, endocrine, metabolic and immune factors. However, in about 50% of cases, no causal factor is identified. The risk of recurrence increases with the number of previous miscarriages (30% in cases where there are two previous miscarriages and 35% in cases where there are three previous miscarriages). The etiologies previously mentioned are considered, in general, causes of clinical abortion, whereas most of the causes of early pregnancy loss remain unexplained.[5]

Successful gestations depend on appropriate trophoblastic invasion and adequate uteroplacental circulation. Changes to this vascular network are related to various pathologies of pregnancy, including: abortions, stillbirth, intrauterine growth restriction (IUGR), pre-eclampsia and placental abruption. Recent studies show that inherited thrombophilia appears to be related to these pathologies, since they interfere with trophoblastic invasion and the placental vasculature.[5]

Table II shows some inherited thrombophilia and their relationship with gestational pathologies.[6]

It is important for obstetricians to be aware of the possibility of an association between hypertension syndromes in pregnancy, particularly the HELLP syndrome (hemolytic anemia, elevated liver enzymes and low platelet count) and inherited or acquired thrombophilia, in order to determine the diagnosis and the most appropriate conduct.[6]

Thrombophilic conditions predisposing to thrombosis are divided into two groups: Primary, inherited or congenital thrombophilia (Antithrombin III deficiency, Protein C and Protein S deficiency, Dysfibrinogenemia, activated protein C resistance/ Factor V Leiden, hyperhomocysteinemia, G20210A mutation in the prothrombin gene, etc.) and secondary or acquired thrombophilia, particularly antiphospholipid antibody syndrome (APLS) *(Table III)*.[7]

In which patients should the search for inherited thrombophilia be performed?[7,8,9]

• All patients with VTE regardless of their age at

TABLE II

Gestational pathologies associated with thrombophilia

Thrombophilias	Abortion	IUGR	Pre-eclampsia	S. HELLP
Antithrombin Deficiency III	++	++	+	–
Protein C deficiency	+	++	+	–
Protein S deficiency	+	++	+	+
Inappropriate fibrinogen synthesis	+	+	–	–
Resistance to activated protein C	+	++	++	–
Factor V Leiden	++	++	++	+
Hyperhomocystenemia	+	+	+	+
Factor II mutation	–	+	–	–
APLS	++	++	++	+
Combined factors	++	++	++	+

onset (before or after 45 years), the circumstances of thrombosis (with or without predisposing factors) or the severity of clinical manifestations;

• The presence of malignant neoplasm is an exclusion criterion, except for hematological neoplasms;

• All women with complications during pregnancy besides VTE:

- Three or more episodes of early foetal loss (first trimester).
- Two or more losses in the second trimester.
- One loss in the third trimester.

• Women with pre-eclampsia and severe IUGR or placental abruption;

• Family or personal history of VTE

- Asymptomatic women with first-degree relatives with thrombophilia
- Asymptomatic women with a family history of VTE should undergo investigation before being prescribed oral contraceptives, hormone replacement therapy, or thinking about getting pregnant.
- Women with previous VTE should undergo screening for the detection of acquired or inherited thrombophilia ideally before getting pregnant.

It is important to point out that if the screening is done during pregnancy or in an event of acute VTE, the diagnosis should be confirmed six months after delivery. Also, when there is deficiency of Vitamin B6, B12 and folic acid, homocystinemia levels are incorrect (acquired hyperhomocystinemia).

THROMBOPROPHYLAXIS DURING PREGNANCY AND PUERPERIUM

During pregnancy, we should consider three phases in which, for different reasons or a combination of factors, make women more predisposed to VTE: The period of pregnancy itself, labor and puerperium (up to six weeks postpartum).

Although it is well-established for the treatment of conditions involving the cardiovascular system, anticoagulation therapy during pregnancy remains controversial. Nevertheless, recognition of APLS puts into question the therapeutic strategy in pregnant women, since it is necessary to prevent thrombosis and foetal loss in this pathology.[10,11]

Thrombophilia in pregnant women is a challenge for the maternal-foetal team. In pregnancy there is an increased risk (six to ten times higher) of VTE, which is higher during puerperium.

Before deciding whether to begin therapy or prophylaxis for the VTE, it is essential to determine the level of risk.

High-risk thrombophilia and those requiring closer monitoring and a more aggressive therapeutic approach are: antithrombin III deficiency, antiphospholipid antibody syndrome, homozygosity for Factor V Leiden and Prothrombin 20210A and combined deficiencies (heterozygosity for Factor V Leiden associated with prothrombin 20210A, among others), *(Tables IV and V)*.

Coumarin-type drugs offer advantages such as oral administration, good availability and easy monitoring. These drugs, however, can cross the placenta and crease a risk of embryopathy (incidence of which is 6%, and occurs during the first trimester of gestation), as well foetal and placental hemorrhage.[11,12]

Heparin does not cross the placenta and is safer to the fetus; however, its variable bioavailability, and the fact that it is difficult to monitor, increase the risk of maternal thrombosis. On the other hand, subcutaneous administration makes it difficult to stick to the course of treatment[12].

TABLE III

Inherited and acquired thrombophilia

Thrombophilia
Inherited:
Factor V Leiden and Resistance to activated protein C
Prothrombin gene mutation
MTHFR gene Mutation
AT III deficiency
Protein C deficiency
Protein S deficiency
Dysfibrinogenemia
Acquired:
APLS
Mixed:
Hyperhomocysteinemia
Increased factor VIII activity
Fibrinogen

TABLE IV

Thrombophilia Major (High Risk)

Major thrombophilias/ high thrombotic risk
ATIII deficit
APLS
Homozygosity for factor V Leiden (FVL) and prothrombin gene (PT20210A)
Combined deficiencies (heterozygosity FVL + PT20210A)
Others

Fractionated heparin (FH) or low molecular weight heparin (LMWH) has revolutionized antithrombotic therapy for pregnant women in recent years. It has various advantages over unfractionated heparins: more antithrombotic and cause less haemorrhagic (more selective inhibitory action on activated factor X than on thrombin); longer half-life with longer intervals of administration; 90% bioavailability in subcutaneous administration; less need to monitor antifactor Xa activity; lower risk of osteopenia and thrombocytopenia (lower platelet activation). In addition to all these advantages, LMWH molecules are large enough to prevent them from crossing the placenta, thereby causing no fetal hemorrhage or teratogenicity. In fact, in recent years, LMWH are considered as an alternative to standard, unfractionated heparin (UFH) and represents a choice in many therapeutic protocols, as follows:[12]

1 – Pregnant women with thrombophilia and no prior VTE should not receive routine prophylaxis, and individual risk classification should be performed *(Table V)*. An exception should be considered when there is antithrombin III deficiency and possible homozygosity of factor V Leiden mutation and the prothrombin gene, since these are high risk thrombophilia and require therapy with LMWH during pregnancy and in the puerperium period *(Table VI)*. In the particular case of antithrombin III deficiency, antithrombin III levels that are less than 30% of the reference values require treatment with antithrombin III concentrate or fresh plasma, to prevent fatal neonatal thrombosis.

Women with inherited or acquired thrombophilia should receive warfarin in the six weeks after delivery, even if they have not received thromboprophylaxis during gestation, if they have other risk factors.

Asymptomatic women with acquired or inherited thrombophilia can be selected for pre- or postnatal thromboprophylaxis, depending on the type of thrombophilia and the presence of other risk factors.

2 – Pregnant women who have thrombophilia that does not fit the categories described in item 1, and who have no history of thromboembolism or no history of poor obstetric prognosis, should not receive prophylaxis with heparin during gestation, which is indicated post-partum in cases of caesarean section. In this situation, anticoagulation therapy should be administered for four to six weeks.

3 – Pregnant women with or without other inherited or acquired thrombophilia (thrombophilia minor) who develop venous thrombosis during pregnancy should receive therapy with LMWH during four months and prophylaxis with LMWH should be continued until the end of the pregnancy. After delivery, oral anticoagulation therapy can begin after overlapping LMWH until therapeutic INR. The duration of anticoagulation therapy will depend on the location and severity of the thromboembolic event.

It has not been proven whether prophylaxis is necessary during pregnancy, particularly in patients with Protein S deficiency; we only know that each case should be analyzed separately.

TABLE V

Assessment of the risk of VT during pregnancy

History of VT	
VTE related to pregnancy or cerebral venous thrombosis or massive PTE or VTE during childhood (<16 years)	6
Spontaneous Proximal PTE or DVT	3
Proximal PTE or DVT induced by transient and identified risk factor	2
Spontaneous distal DVT	2
Distal DVT induced by transient and identified risk factor	1
In case of previous existing venous thrombosis	
History of recurrent VTE	3
Residual vein thrombosis	3
Recent history of VTE (< 2 years)	2
Confirmed hypercoagulability	
Antithrombin III deficiency, lupus anticoagulant, antiphospholipid antibodies	6
Combined thrombophilia	3
Protein C deficiency, protein S deficiency, heterozygosity Factor V Leiden Mutation, heterozygosity Prothrombin G20210A mutation	1
Absence of confirmed hypercoagulability, but family history of recurrent and serious VTE	1
Risk factors related to current pregnancy	
Bedrest, immobilization	2
Multiple pregnancy	1
Aged over 35	1
Obesity (body mass index above 30)	1
TOTAL SCORE: < 3 Thromboprophylaxis is not necessary 3 – 5 Thromboprophylaxis only in the third trimester ≥ 6 Start thromboprophylaxis immediately	
Dargaud e Col. Int J Gynecol Obst 2005;90:203-207	

4 – If hyperhomocystenemia is the sole coagulation defect, supplementation with vitamins B6, B12 and folic acid should be done before and throughout pregnancy. Although there are no clinical trials to support this approach, the toxicity of this therapy is null, while on the other hand, folic acid has the advantage of reducing the occurrence of neural tube defects. We should consider the use of LMWH in pregnant women with hyperhomocystenemia, whose levels do not decrease with the administration of vitamins, if there is a history of thromboembolism, or in the presence of obstetric complications typical of thrombophilia.

5 – APLS - While this syndrome is a treatable cause of foetal loss, the treatment of APLS during pregnancy is still controversial, mainly due to the lack of prospective controlled clinical trials. The regimens evaluated to date include the use of aspirin, heparin, prednisolone and globulin.[12,13] As a general rule, pregnant women with antiphospholipid antibodies without any manifestation arising from or attributable to these antibodies, are not treated with prophylaxis. However, in the presence of high anticardiolipin antibody titers, 100 mg of aspirin per day may be prescribed as an anti-platelet, provided there is no contraindication. For patients with recurrent vascular thrombosis symptoms, initial anticoagulation therapy with LMWH should be administered, then

TABLE VI

Therapeutic and prophylactic doses of LMWH during pregnancy

Prophylaxis	Enoxaparin (100 U / mg)	Dalteparin	Tinzaparin
Normal weight (50–90 kg)	40 mg / day	5000 units / day	4500 units / day
Weight < 50 kg	20 mg / day	2500 units / day	3500 units / day
Weight > 90 kga	40 mg 12-12 hours	5000 units 12-12 hours	4500 units 12-12 hours
Higher prophylactic doses	40 mg 12-12 hours	5000 units 12-12 hours	4500 units 12-12 hours
Therapeutic dose	1 mg/kg 12-12 hours	90 units / kg 12-12 hours	90 units / kg 12-12 hours
Body mass index > 30 at the start of pregnancy			

oral anticoagulants should be maintained indefinitely, maintaining INR between 3.0 and 3.5. For recurrent abortions, aspirin 100mg/day is recommended from the beginning to the 12th week of gestation, and then LMWH until six weeks after the resolution of the pregnancy. The use of corticosteroids associated with this regimen is justifiable in two situations: (1) when the APLS is secondary to other existing diffuse connective tissue disease, and (2) when the platelet count is lower than 70,000/mm, in order to increase platelet count. The replacement of oral anticoagulants by heparin is mandatory in pregnancy due to the teratogenic effects of the oral anticoagulants. Intravenous δglobulin and plasmapheresis were used in few cases for the treatment of recurrent abortions, despite the conventional anticoagulation therapy. Nevertheless, the high cost and lack of well-conducted studies do not enable us to draw any conclusion as to its effectiveness.[12,13]

The current therapeutic strategy that has been gaining more supporters is the use of LMWH associated with aspirin 100 mg/day. Thus, women with APLS and previous thrombosis or obstetric complications should receive, in addition to aspirin at low doses (initiated preferably in the preconception period), therapeutic doses of LMWH during pregnancy and postpartum (6-8 weeks). Due to the risk of arterial thrombosis, anti-platelet aggregation with aspirin or another blood thinner, such as clopidogrel, should be maintained in the long term. Some studies show that with this regimen, obstetric results related to APLS, in terms of the frequency of fetal survival rate, increased from 19% to 70%.[13]

Treatment of APLS in pregnancy with corticosteroids or intravenous immunoglobulin did not show better effectiveness than those previously mentioned.

Contraception in patients suffering from this syndrome is very important, given the poor perinatal outcome. The use of an intrauterine device is recommended (although there is a risk of infection during corticosteroid therapy), as well as avoiding the use of oral hormone contraceptive based on oestrogen as it leads to an increased risk of thromboembolism. Therefore, progestogen contraceptives ("the pill") are allowed, and tubal ligation is recommended in cases of severe nephropathy or systemic disease. In the differential diagnosis of this syndrome, if there is a family history of thrombosis, an assessment of inherited thrombophilia should be performed.[14]

6 – Another situation that may raise questions about the approach relates to ***pregnant women with a history of venous thrombosis with well identified transient risk factor who, after investigation, did not have thrombophilia.*** In these cases, only prophylaxis with LMWH should be administered, within six weeks after delivery. The need of thrombophylaxis during pregnancy in these women is controversial. There is evidence that if previous VTE was associated with a transient risk factor, such as trauma, thrombophylaxis is not necessary. However, if previous VTE was associated with an oestrogen-related risk factor, such as the use of oral contraceptive or pregnancy, or if there is another risk factor such as obesity, thromboprophylaxis is indicated.

Women without thrombophilia, but with previous VTE, should receive thromboprophylaxis with LMWH during puerperium.

It is reasonable to administer thromboprophylaxis to pregnant women who previously had only one episode of VTE associated with a known risk factor that has been resolved.

TABLE VII

Approach to Thrombophilia Major

Major thrombophilias / high thrombotic risk: Approach	
Asymptomatic No thrombotic or obstetric history	Obstetric history Two or more spontaneous thrombotic events One serious spontaneous event (near fatal pulmonary embolism; cerebral, mesenteric or superior vena cava thrombosis)
Pre-conception: ASA (APLS) Pregnancy: ASA (APLS) LMWH (therapeutic) Postpartum: LMWH (therapeutic) or oral anticoagulant six to eight weeks Indefinite antiplatelet therapy (APLS)	Pre-conception: ASA (APLS) Pregnancy: ASA (APLS) LMWH (therapeutic) Postpartum: LMWH (therapeutic) or oral anticoagulant Six to eight weeks, consider indefinite Antiplatelet therapy (APLS)

Women with previous recurrent VTE and a family history of VTE in a first degree relative should receive thromboprophylaxis with LMWH during pregnancy and at least six weeks after delivery.[15]

7 – Recent evidence recommends that pregnant women ***with thrombophilia and previous VTE*** receive thromboprophylaxis during pregnancy and six weeks after delivery. In the case of ATIII deficiency, the prophylactic doses of LMWH should be increased. *(Table VI)*.

AGENTS USED IN THE TREATMENT AND PROPHYLAXIS OF VTE DURING PREGNANCY

Low molecular weight heparins (LMWH)

These are the agents of choice for thromboprophylaxis in pregnancy. They are as effective as and safer than unfractionated heparin (less risk of thrombocytopenia and osteoporosis).

They can cause allergic skin reactions, which may require their replacement by another heparin formulation, or even heparinoids.

Current studies have shown that it is not necessary to dose the levels of anti Xa activity in pregnant women with normal renal function when LMWH is used in prophylactic doses. In the particular case of deficiency of AT III, it is important to monitor anti Xa, because sometimes it is necessary to increase the dose of LMWH.

Although the risk of LMWH-induced thrombocytopenia is negligible, the current guidelines recommend determining platelet count one week after thromboprophylaxis begins.

In women who, as a consequence of a previous VTE, have been using oral anticoagulants chronically, higher prophylactic doses or therapeutic doses of LMWH should be administered.

LMWH is the most appropriate choice agent for postpartum thromboprophylaxis in women who received LMWH during gestation, or who require only three to five days of therapy postpartum.[15]

Low dose aspirin

Low doses of aspirin are safe in pregnancy; however, there are no studies recommending its use in isolation for thromboprophylaxis in general.

100 mg aspirin associated with LMWH is currently recommended for thromboprophylaxis in cases of APLS.[15]

Oral anticoagulants

Oral anticoagulants should be avoided during pregnancy, particularly between week 6 and 12 of gestation, due to the associated risk of teratogenicity

TABLE VIII

Approach to thrombophilia Minor

Minor thrombophilias / moderate thrombotic risk: approach	
Absence of previous thromboembolic events or adverse complications during pregnancy	Previous thromboembolic event Adverse complications during pregnancy
Pregnancy: No treatment is needed If other risk factors exist, consider LMWH (Prophylaxis) Postpartum: In case of c-section, history in first-degree family member or other risk factors, LMWH (prophylaxis) Six to eight weeks	Pregnancy: LMWH (Prophylaxis) If other risk factors exist, LMWH (therapeutic) Postpartum: LMWH (Prophylaxis) Six to eight weeks

(5%), abortions, foetal and maternal hemorrhage and neurological problems.

In fact, oral anticoagulants may cause placental abruption, a characteristic embryopathy, as well as central nervous system (CNS) alterations and foetal hemorrhage. Warfarin embryopathy is characterized by nasal hypoplasia and/or non-consolidation of epiphysis, and it is associated with exposure to warfarin between weeks 6 and 12 of gestation. Alterations in CNS include dorsal midline dysplasia, with agenesis of the corpus callosum, atrophy of the cerebellar midline, ventral midline dysplasia with optic atrophy and amaurosis, and hemorrhage. Unlike warfarin embryopathy, which has been documented only in the first trimester, CNS alterations may occur after exposure to warfarin in any stage of the gestation. While the incidence of these CNS alterations appears to be low (<5%), the long-term sequelae are more devastating than those associated with warfarin embryopathy. When warfarin is used continuously throughout gestation, the trauma of birth can lead to significant foetal hemorrhage. Therefore, warfarin should not be used in the first trimester or the end of the third trimester, and some authors do not recommend its use at any stage of gestation.

Warfarin does not pass into the breast milk, so it is safe for breastfeeding women. However, due to the risk of postpartum hemorrhage and perineal haematoma, INR should be monitored. Therefore, in the cases which only three to five days of thromboprophylaxis are necessary, LMWH are indicated rather than oral anticoagulants.

When warfarin is opted for, its administration should begin in the second or third day after delivery, and it should be maintained in association with LMWH (which should begin soon after delivery) until INR > 2.0 for two consecutive days.[15]

Elastic compression stockings

Elastic compression stockings can be used during pregnancy and in weeks 6 to 12 postpartum, particularly by women with a history of VTE, thrombophilia in bedridden patients, or when traveling.[15]

CARE NEEDED IN THROMBOPHYLAXIS, DURING LABOR AND AFTER DELIVERY

All pregnant women receiving LMWH and going into labor should be advised to discontinue the respective LMWH and go to the hospital or maternity, from where therapy should be guided by the medical team.

Prothrombotic coagulation changes associated with pregnancy are the highest immediately after delivery, so thromboprophylaxis should continue in the puerperium period. The postpartum doses should be administered according to the type of LMWH: enoxaparin 40 mg, dalteparin 5000 iu, tinzaparin 50 units/kg.

Epidural anesthesia should be discussed with the anesthesiologist. It is important to discuss with the women, before the delivery, the implications of the treatment with LMWH for epidural and spinal anesthesia. To minimize the risk of epidural haematoma, epidural anesthesia should not be given within 12 hours of discontinuing prophylactic LMWH, or

within 24 hours in the case of therapeutic LMWH. LMWH administration should not begin within four hours after insertion or removal of an epidural catheter, and cannula should not be removed within 10-12 hours of the latest injection of LMWH. In the case of a cesarean section, the risk of haematoma is 2%; pregnant women should receive a prophylactic dose of LMWH on the day before the cesarean section; she should not receive it on the morning of the cesarean section, and it should be restarted at least three hours after the cesarean section, or four hours after insertion or removal of the epidural catheter.

Women with high risk of hemorrhage, with risk factors such as major hemorrhage in pregnancy, coagulopathy, progressive wound haematoma, suspected intra-abdominal hemorrhage and postpartum hemorrhage can be better controlled with unfractionated heparin. Unfractionated heparin has a shorter half-life than LMWH, and there is greater experience with protamine sulfate to reverse its activity.

If, during thromboprophylaxis, the woman develops hemorrhage, LMWH should be discontinued. It is important to remember that excessive blood loss and blood transfusion are risk factors of VTE, therefore thromboprophylaxis should begin, or be resumed as soon as the immediate risk of hemorrhage is reduced.[16] ■

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