VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PREGNANCY AND PUERPERIUM

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1. INTRODUCTION

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is one of the main causes of maternal morbidity and mortality in developed countries. The incidence ranges between 0.5 and 3 per 1000 pregnancies. DVT has the same frequency among the three trimesters, in contrast to PE that is more frequent during the postpartum period.

More than 50% of women with a thrombotic accident during pregnancy, present congenital or acquired thrombophilia. **The risk of recurrence of VTE during pregnancy in women with a previous occurrence is about 7-12%. With heparin therapy, the risk of recurrence decreases until 1-1.5%.**

Apart from physiological changes during pregnancy predisposing the pregnant woman to a thromboembolism event, some risk factors can exist (pre-existing or new, pregnancy-related) that significantly increase the risk of VTE (Table 1).

During pregnancy there are some changes that affect Virchow's triad and predispose the pregnant woman to VTE.

There is a hypercoagulability state secondary to the increase of coagulation factors (II, V, VII, VIII, IX, X, XII and fibrinogen) and to the decrease of inhibitors' action (decrease of S protein and increase of C activated protein resistance); moreover, there is a decrease of fibrinolysis secondary to the increase of the inhibitor of plasminogen 1 and 2 activation and the increase of platelet aggregation.

In the lower limbs there is an increment of venous stasis with a decrease of 50% of venous flow during the third trimester, because of the mechanical action of the uterus and the action of progesterone in the vascular musculature that increases the compliance and decreases venous tone.

There is also endothelial activation and vascular injury during delivery.

Table 1. Thromboembolism risk factors during pregnancy

Preexisting	During pregnancy

• Any previoust VTE
• Congenital thrombophilia
  • Protein C deficiency
  • Protein S deficiency
  • Antithrombin deficiency
  • Protein C Resistance (Factor V Leiden)
  • Dysfibrogenemia
  • Prothrombine gene mutations (G20210A)
• Primary or secundary antiphospholipid syndrome
• Age >35 años
• Obesity (BMI>30Kg/m^2) before or at beginning of gestation
• Parity ≥ 3
• Smoker
• Gross varicoses veins
• Paraplegia
• Sickle cell disease
• Inflammatory disease (Sistemic lupus erithematosus, inflamatory poliarthropathy, inflamatoria, inflamatory bowel disease)
• Medical comorbidities (nephrotic syndrome, congenital heart disease, heart failure)
• Type I Diabetes Mellitus with nephropathy
• Mieloproliferative disorders
• Cancer
• Parenteral drug addiction
	• Surgery during pregnancy or postpartum (abortion, postpartum sterilisation)
	• Hyperemesis
	• Dehydration
	• Ovarian hyperestimulation Syndrome
	• Current systemic infection
	• Immobility (3 days in bed)
	• Preeclampsia
	• Postpartum haemorrhage (>1 litre) with transfusion
	• Prolonged labour (>24 horas)
	• Cesarean
	• Operative delivery
	• Multiple gestation
	• Long travels (>4 horas)
	• Stillbirth in current pregnancy
	• Preterm birth (<37 weeks)

2. INDICATIONS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PREGNANCY AND PUERPERIUM

Venous thromboembolism prophylaxis is a controversial topic. Most recommendations are based on retrospective studies and expert opinion, therefore there is a low level of evidence.

Thromboprophylaxis in pregnant women must be assessed for each one individually. It depends on risk factors, previous event of thrombosis and diagnosis of congenital or acquired thrombophilia. A multidisciplinary management by an obstetrician and haematologist is required.

All pregnant women should be assessed for risk of thromboembolism at different moments:

- Preconception period or first weeks of gestation if possible

- In first obstetrical appointment regardless of gestational age
- Hospital admission: assess the risk if it was not assessed before, or reassessment according to circumstances.
- Intercurrent condition during pregnancy.
- During labour and early postpartum

It is also necessary to assess the risk-benefit of anticoagulant treatment taking into account the fetus and mother's effect and choosing the most suitable dose.

To simplify, different possible situations where thromboprophylaxis is indicated during pregnancy and postpartum are presented (Table 2)

A. PREGNANT WOMEN **WITH NO** VTE **OR** THROMBOPHILIA
   A.1 General aspects
   A.2 Post-caesarean section prophylaxis
   A.3 Hospital admission

B. PREGNANT WOMEN **WITH** VTE **AND/OR** THROMBOPHILIA
   B.1 VTE and no thrombophilia
   B.2 VTE and thrombophilia
   B.3 No VTE and inherited thrombophilia
   B.4 Acquired thrombophilia (antiphospholipid syndrome)
   B.5 Anticoagulant treatment (with or without thrombophilia)

Table 2. Indications for VTE prophylaxis

NO antecedents VTE NO thrombophilia		WITH antecedent VTE AND/OR thrombophilia			
Prophylaxis	Hospital admission	VTE antecedent NO thrombophilia	VTE antecedent WITH thrombophilia	Thrombophilia NO VTE	Anticoagulant treatment
Gestation: ≥4RF antenatal LMWH At least 6 weeks postpartum ≥3RF start LMWH from 28weeks If COVID ≤ 4 weeks and < 4 RF LMWH 10 days at discharge Postpartum: • ≥3 RF • Obesity • Emergency cesarean or cesarean during labour. LMWH 10 days • COVID ≤ 4weeks At least 6 weeks postpartum	• From the 3rd day • If COVID ≤ 4 weeks Start LMWH At discharge consider according risk factors	Recurrent: Antenatal high-prophylactic or therapeutic dose until 6-8 weeks postpartum Unique realted with temporal factor WITHOUT RF Consider from 28 w (prophylactic dose) to 6-8 w postpartum Unique related with temporal factor WITH RF or estrogen-related, unusual localisation or without trigger factor. LMWH prophylactic dose At least 6-8 w postpartum	Antenatal LMWH At least 6-8 w postpartum high-prophylactic or therapeutic doses	Antenatal prophylactic dose. At least 6-8 w postpartum If FVL mutation or heterozygous prothrombine gene mutation: - NO RF: prophylactic LMWH in postpartum - IF RF: prophylactic LMWH from 28 w to 6-8 w pospartum	STOP VKA <7w Start therapeutic LMW Reintroduce AVK at 2nd-3rd day postpartum

A. PREGNANT WOMEN WITH NO VTE OR THROMBOPHILIA

A.1 General aspects

The indication for thromboembolism prophylaxis depends on the number of associated risk factors (globally referred to in Table 1).

There are different guidelines about thromboprophylaxis following different criteria for the use of anticoagulant therapy. Depending on the criteria followed, prophylaxis is indicated from 30% to 80% of population. According to ACOG (*American College of Obstetricians and Gynecologist)* anticoagulant therapy is indicated in 1% of populations in contrast to 35% according to the ACCP (*American College of Chest Physicians)* and 85% following RCOG guidelines (*Royal College of Obstetricians and Gynecologists*).

In these guidelines, different criteria have been adapted in an attempt to avoid systematic overtreatment and to simplify the management and ensure compliance to treatment.

The scheme proposed by the RCOG has been followed but considering that those postpartum circumstances predisposing to VTE with an OR ≥ 5 represent an intermediate risk and are therefore an indication for thromboprophylaxis for 10 days postpartum. In contrast, in low-risk situations, we will need ≥ 3 factors (instead of 2) to recommend postpartum thromboprophylaxis.

Annex 1 'Antenatal risk factors and thromboprophylaxis' and Annex 2 'Birth/postpartum risk factors and thromboprophylaxis' describe the strategy for prophylaxis during pregnancy and postpartum according to risk factors.

In general:

- **During pregnancy**, in the presence of **4 or more antenatal low-risk factors**, **prophylactic treatment with LMWH is indicated antepartum and up to 6 weeks postpartum** (for more details, see Annex 1). In the presence of **3 low-risk factors, prophylactic treatment with LMWH is indicated from 28 weeks of gestation and up to 6 weeks postpartum.**

- In case of **vaginal delivery with < 3 low risk factors and a good puerperal course**, mobilisation and the recommendation to wear strong compression stockings during the first and second week postpartum are considered adequate thromboembolic prophylaxis measures.

- In those postpartum circumstances with a higher risk of thrombosis, such as obesity with BMI < 30 and maternal age > 35 years, mobilisation and the use of strong compression stockings are important, but prophylaxis with LMWH for 10 days postpartum is also a good option. In those postpartum women with obesity with **BMI ≥ 30** as an individual factor, LMWH prophylaxis for 10 days postpartum is also a good option. However, in cases of **BMI ≥ 40**, LMWH prophylaxis for 10 days postpartum is indicated.

- In the **postpartum** period, if the patient has **3 or more low-risk factors or 1 intermediate risk factor**, postpartum prophylaxis with **prophylactic LMWH** is indicated **until completion of 10 days** of treatment. If **more than 3 intermediate risk factors** are present, prolongation of postpartum prophylaxis with **prophylactic LMWH for 6 weeks postpartum** is indicated.

A.2. Post-caesarean section prophylaxis:

The risk of postpartum thrombosis for elective caesarean section is higher than for vaginal delivery (OR 2.3). The thrombotic risk is even higher in cases of emergency caesarean section or during labour (OR of 3.7).

Therefore, LMWH prophylaxis is recommended for all patients undergoing **emergency caesarean section or in labour** for 10 days postpartum**.**

In cases of **elective caesarean section,** LMWH prophylaxis is indicated if ≥ 2 thrombotic risk factors are present, for 10 days.

Strong compression stockings are recommended during the first and second week postpartum in patients with ≥ 4 risk factors antenatally or ≥ 2 risk factors postpartum (Annex 1 and 2).

A.3. Hospitalisation:

Hospital admission during pregnancy is associated with an 18-fold increased risk of VTE compared to the out-of-hospital risk. The risk remains elevated after discharge, being 6 times higher at 28 days post-discharge. In the third trimester and in patients older than 35 years there is a higher risk. The risk of VTE during hospitalisation and post-discharge is 4 times higher if admission is less than 3 days, and 12 times higher if admission lasts 3 or more days.

For this reason, **LMWH prophylaxis is recommended for patients from the third day of hospital admission**, regardless of the number of risk factors. At discharge, risk factors should be reassessed (Annex 1 and 2) to decide whether it is necessary to continue prophylaxis at home.

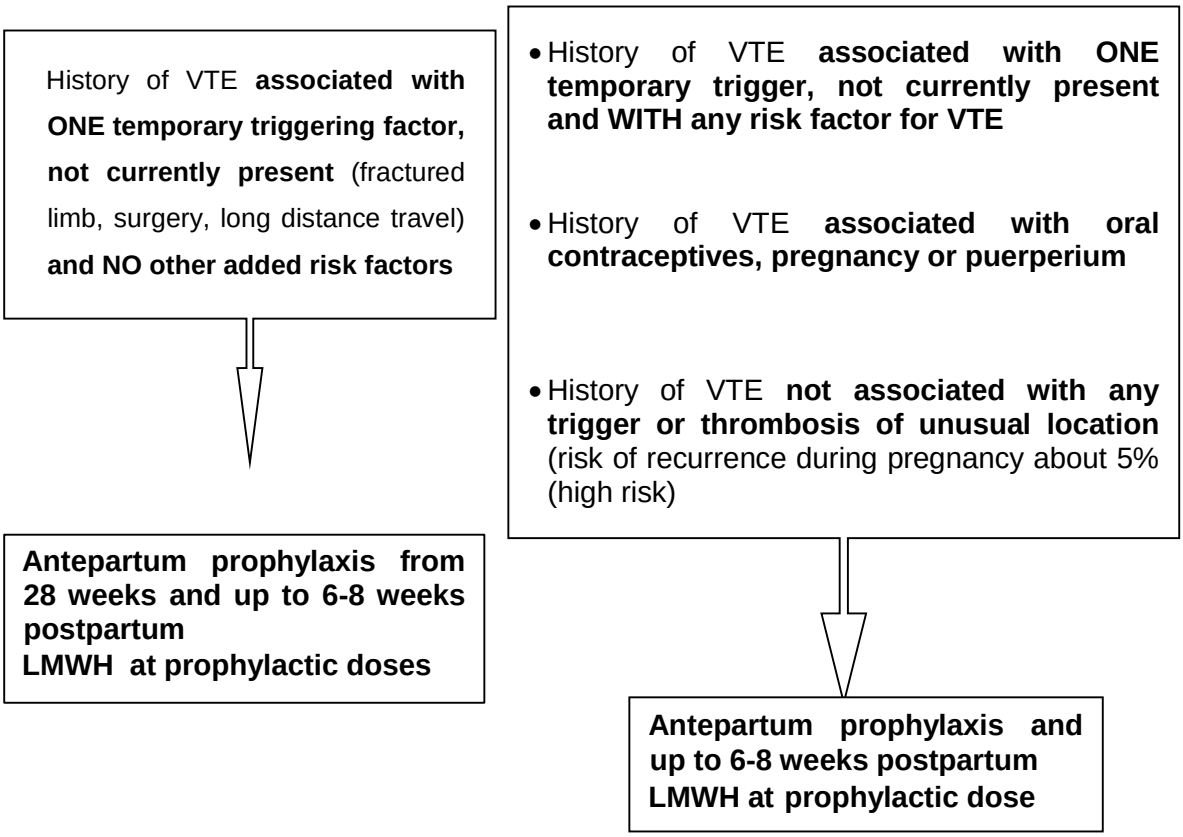
B. PREGNANT WOMEN WITH A HISTORY OF VTE AND/OR THROMBOPHILIA

B.1 Patients with a history of VTE and no thrombophilia:

Within this group is a range of patients with varying degrees of thrombotic risk and therefore need to be stratified into different subgroups:

B.1.1. Patients with a history of ONLY ONE episode of VTE:

In this case, treatment will depend on the factors associated with the thrombotic episode



B.1.2. Patients with recurrent VTE:

Pregnancy in these patients may carry a high risk of recurrence. Many of these patients can be expected to be on long-term anticoagulant therapy, in which case it will be continued during pregnancy (see section 2.5). If pregnancy is initiated without anticoagulant therapy, initiation of treatment with ***high prophylactic or therapeutic*** (weight-adjusted) ***doses of LMWH*** re indicated as soon as pregnancy is diagnosed and up to 6-8 weeks postpartum.

B.2. Patients with a history of VTE and thrombophilia:

In all cases, ***antepartum prophylaxis (LMWH at prophylactic doses) and postpartum prophylaxis (LMWH at prophylactic doses for 6-8 weeks)*** is indicated. In patients with thrombophilia considered to be at increased thrombotic risk (such as antithrombin deficiency, protein C and S deficiencies, homozygous prothrombin or factor V Leiden gene mutations and patients with combined deficiencies - more than one associated thrombophilia), ***treatment with high prophylactic or therapeutic*** (weight-

adjusted) ***doses of LMWH*** is recommended as soon as pregnancy is diagnosed and for up to 6-8 weeks postpartum.

B.3. Patients with no history of VTE and with hereditary thrombophilia

Increasingly, patients with inherited thrombophilic disorders detected by family investigation initiated after diagnosis in a symptomatic family member are seen in consultations. The risk of VTE in pregnant women with a thrombophilia varies considerably depending on the type of thrombophilia. Therefore, pregnant women should be stratified according to the level of risk associated with their thrombophilia.
In protein C deficiency, protein S deficiency, antithrombin deficiency, homozygous factor V Leiden, homozygous prothrombin G20210A mutation and combined deficiencies (combinations of 2 or more thrombophilia, both high and low risk), ***antepartum (LMWH at prophylactic doses) and postpartum (LMWH at prophylactic doses for 6 - 8 weeks) prophylaxis will be performed***.
In the remaining thrombophilia (heterozygous factor V Leiden, heterozygous prothrombin gene mutation), ***postpartum prophylaxis*** (LMWH at prophylactic doses for 6-8 weeks) will be performed, with antepartum prophylaxis being reserved from week 28 in those cases associated with a risk factor.

B.4. Pregnant women with acquired thrombophilia (antiphospholipid syndrome):
The recommendations on the management of this type of patient are set out in a specific protocol

B.5. Patients on long-term anticoagulant treatment with vitamin K antagonists (VKA) (with or without thrombophilia):
It is recommended that treatment with VKA be discontinued before 7 weeks of gestation, due to the risk of teratogenicity, and that treatment be switched to ***LMWH at therapeutic doses***. At 13 weeks, depending on the case, it is assessed whether to continue with heparin or to switch back to VKA, in which case treatment should be changed back to LMWH at 36 weeks or earlier if there is a risk of the patient going into labour. On the second or third day postpartum, if there are no complications, it is possible to restart VKA treatment. The Haemostasis Service will be contacted to establish the appropriate transition and regimen.

3. THERAPEUTIC MEASURES AND PHARMACOLOGICAL THERAPY

3.1 Anti-embolism stocking
They are indicated in the following cases:

- As an alternative to LMWH (in cases where its use is contraindicated or not available) in hospitalised patients with thromboprophylaxis criteria
- Post-caesarean hospitalised patients at risk of VTE (in combination with heparin if required)
- Risk of VTE (pregnant women with more than 3 risk factors for VTE)
- History of VTE (in combination with heparin if required)
- Prolonged travel of more than 4 hours of duration

3.2 Low Molecular weight heparin (LMWH):

Although scientific evidence in pregnant women is scarce, in non-pregnant women there is sufficient evidence to indicate that treatment with LMWH is at least as effective and is associated with lower mortality and a lower rate of haemorrhagic complications than treatment with UFH. Also, the risk of osteoporosis and thrombocytopenia is lower. Allergic skin reactions, although rare, may occur during LMWH treatment, requiring a change of heparin or the use of a heparinoid.

LMWH have more predictable pharmacokinetics and a longer half-life than UFH. In contrast, TTPa does not correlate with the anticoagulant effect and is therefore not useful in monitoring treatment. As pregnancy progresses and the patient gains weight, the dose should be adjusted (always with the same goal of full doses). Such adjustment can be done simply according to the patient's increasing weight or, if desired, adjusted to antifactor Xa levels 3-4 hours after the morning dose. The goal is to obtain antifactor Xa levels between 0.5-1.2 U/ml.

Monitoring of antifactor Xa levels is not generally necessary, except in patients whose weight is at the extremes (<50 kg or >90 kg), in patients at very high thrombotic risk and in patients with impaired renal function. In these cases, contact the Maternal-Fetal Medicine specialist for specific management together with the haematology department.

Table 3 shows the doses and types of LMWH most commonly used during pregnancy.

Like UFH, LMWH does not cross the placenta and is not secreted into milk, making it safe for the foetus during pregnancy and breastfeeding.

Table 3. Dose and types of LMWH used during pregnancy.

Weight	Enoxaparin	Dalteparin	Tinzaparin
< 50 Kg	20 mg daily	2500 units daily	3500 units daily
50-90 Kg	40 mg daily	5000 units daily	4500 units daily
91-130 Kg	60 mg daily*	7500 units daily	7000 units daily*
131-170 Kg	80 mg daily*	10000 units daily	9000 units daily*
> 170 Kg	0,6 mg/Kg/day*	75 UI/Kg/day	75 u/Kg/day*
High prophylactic dose	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly
Therapeutic dose	1 mg/Kg/12 hourly	100 u/Kg/12 hourly	90 u/Kg/12 hourly 175 u/Kg/24 hourly

* May be given in 2 divided doses

LMWH and free fetal DNA testing

Studies show that a fetal DNA fraction of approximately 2-4% is necessary to have an accurate free fetal DNA result. It is well known that obesity, maternal hypertension, early gestational age and fetal aneuploidy are associated with a low fetal fraction. Most of the free fetal DNA in maternal blood originates from apoptosis of placental trophoblasts. Recent studies suggest that LMWH reduces trophoblast apoptosis through complex mechanisms, and this may be associated with repeated failures of free fetal DNA tests for low fetal fraction in patients on treatment with LMWH as well as aspirin and prednisolone. Therefore, in patients on LMWH treatment with an indeterminate low fetal free fetal DNA test result, the case should be re-evaluated with the specialist team.

3.3 Low dose aspirin

The administration of low-dose ASA in the second and third trimester is safe for both mother and fetus. Low doses are defined as doses not exceeding 200 mg/d. There seems to be general agreement on the use of low-dose ASA in conjunction with LMWH in thrombophilia with an increased risk of arterial thrombosis in addition to venous thrombosis (antiphospholipid syndrome). In contrast, there is no evidence of the usefulness of low-dose ASA in VTE prophylaxis during pregnancy.

3.4 Unfractionated heparin (UFH)

UFH is safe for the fetus and newborn as it does not cross the placenta and is not secreted into the milk.

The dose of UFH should be adjusted by haematology according to the activated partial thromboplastin time (aPTT) values obtained 6 hours after heparin administration, with values between 1.5 and 2.5 times the control value or between 48-108 seconds being considered normal, although this depends on the technique used in each laboratory.

The main side effects that affect the mother and are:

a) Bleeding: a 2% risk of bleeding has been reported when administered at therapeutic doses. During pregnancy, aPTT elongation is decreased probably due to increased levels of factor VIII and fibrinogen.

b) Osteoporosis: long-term treatment (3-6 months) with UFH has been associated with 2-3% vertebral fractures and a decrease in bone mass in up to 30% of patients.

c) Thrombocytopenia. heparin type II-induced thrombocytopenia is a rare but potentially life-threatening adverse effect of UFH treatment. Autoimmune in aetiology, it is associated with a prothrombotic state and may be accompanied by extension of a pre-existing DVT or new arterial or venous thrombosis. When it develops, it usually appears between 5 and 12 days after the start of treatment. It is important to differentiate this condition from transient thrombocytopenia, which usually appears within the first 5 days of treatment, is reversible and does not require discontinuation of treatment. A platelet count is recommended 5 to 15 days after starting heparin treatment. If platelet counts are below 100 x 10^9/L or less than 50% of baseline, it is recommended to discontinue heparin and contact the Haemotherapy and Haemostasis Service for specific tests.

3.5 Vitamin K antagonist oral anticoagulants

VKA oral anticoagulant crosses the placenta and has teratogenic and embryotoxic effects on the fetus. Administration between 6-12 weeks may cause skeletal embryopathy in 5% of patients, increasing the risk of miscarriage. From 13 weeks onwards it seems safe, and the risk-benefit ratio should be considered. In pregnant women with mechanical valves, VKA can be reintroduced from the second trimester onwards to achieve optimal International Normalised Ratio (INR) levels.

There is a risk of fetal haemorrhage, a rare but possible effect at any time during pregnancy, especially at the time of delivery: it is therefore important to switch to LMWH at around 36 weeks or if there is a suspicion of preterm labour.

It is not secreted in the milk and can therefore be administered during breastfeeding. In patients who decide to use VKA postpartum, administration can be started 2-3 days post-delivery after contacting the Haemostasis Service to establish the transition and appropriate regimen.

Administration of LMWH should be maintained until the INR is between 2 and 3. The appropriate dose will be that which maintains an INR between 2 and 3 or, in cases of very high risk, between 2.5 and 3.5. When VKA is used, it will be necessary to carry out regular INR controls.

4. ANTICOAGULATION MANAGEMENT IN LABOUR . ANAESTHESIA CONSIDERATIONS

All pregnant women under treatment with anticoagulants should be scheduled for a visit to the anaesthesia department. The use of epidural anaesthesia should be agreed with the anaesthesiologist and discussed with the patient, explaining the risks involved (risk of compression due to haematoma). The patient on anticoagulant treatment should be warned during prenatal visits that if she goes into or thinks she may go into spontaneous labour, she should stop taking heparin and go to the hospital for medical assessment. After examination, the physician will decide whether the patient is in labour, whether or not to continue treatment, and the dose to be given. Table 4 describes the precautions regarding the use of peripartum LMWH and the use of locoregional analgesia.

If the patient goes into labour spontaneously:

- In case of prophylactic doses of heparin, epidural analgesia can be administered 12 hours after the last dose.
- Patients who require therapeutic doses of heparin during pregnancy (e.g. recent thrombosis or mechanical prosthesis wearers) benefit during the intrapartum period from the switch to intravenous UFH because of its shorter half-life (1.5 hours) and the greater efficacy of protamine sulphate in reversing its effects.

  Protamine sulphate is a protein that neutralises the anticoagulant effect of heparin. It has a rapid effect and persists for up to two hours. In the case of UFH, it reverses its effect 100%, in contrast to LMWH where it only reverses its effect by 80%. The dose to be administered depends on the dose of heparin used, in general terms 1 mg of intravenous of protamine sulphate neutralises 100 IU of heparin. It is important not to exceed a dose of 50 mg in 10 minutes. The following side effects have been described: hypotension due to histamine release, hypersensitivity or anaphylaxis, pulmonary hypertension, non-cardiogenic pulmonary oedema, thrombocytopenia and impaired platelet aggregation
- In patients on VKA treatment who have not previously switched to heparin, a caesarean section is indicated due to the risk of fetal haemorrhage. Treatment with VKA should be discontinued 4-6 weeks before the expected delivery date and replaced with LMWH or UFH
- The administration of low-dose acetylsalicylic acid (ASA) alone does not contraindicate the technique of locoregional analgesia.

In case of scheduled caesarean section or induction of labour:

- Heparin treatment should be discontinued in those patients on prophylactic doses 12 hours before the scheduled time
- In those patients on treatment with therapeutic doses of LMWH, should be changed to prophylactic doses the day before induction or caesarean section. On the day of caesarean

section, treatment should be discontinued. Some degree of thromboprophylaxis can be obtained by wearing elastic stockings. The therapeutic dose should be restarted after 12-24 hours. Likewise, in caesarean sections it is advisable to leave drains in the wall due to the risk of haematoma at this level (2% with heparin) and to perform discontinuous suturing of the skin.

Table 4. Special consideration of heparin management in relation to labour

LABOUR MANAGEMENT	
LMWH or ASA with bleeding or contractions	STOP LMWH or ASA
LMWH therapeutic dose	locoregional analgesia >24h last dose
LMWH prophylactic dose	locoregional analgesia >12h last dose
UFH	Discontinue 4-6h before or Protamine sulphate
Low-dose ASA	No contraindication to locoregional analgesia.
Re-start postpartum LMWH	At 12-24 hours and at least 6 hours after removal of the catheter, in the absence of bleeding

5 PRECAUTION ABOUT ANTICOAGULANT USE

LMWH should not be administered or should be discontinued in patients at risk of haemorrhage after a proper risk/benefit assessment. Haemorrhagic risk factors are:

- Active antepartum or postpartum haemorrhage
- Increased risk of haemorrhage (placenta praevia)
- Haemorrhagic diathesis (von Willebrand disease, haemophilia or acquired coagulopathy)
- Thrombocytopenia less than 75 x 10^9 /L
- Ischaemic or haemorrhagic stroke within the last 4 weeks
- Renal failure (glomerular filtration rate < 30 ml/minute/1. 73 m2)
- Severe liver disease (Abnormal prothrombin time)
- Uncontrolled hypertension (TAS > 200 mmHg or TAD > 120 mmHg)

6. INDICATIONS FOR THROMBOPHILIA TESTING

There is currently no evidence in favour of universal screening for thrombophilia during pregnancy. Screening has to be selective and its indications are:

a) History of thrombosis

b) Family history of thrombophilia in 1st degree relatives

c) Patients with pre-eclampsia or early onset (less than 34 weeks) or recurrent IUGR.

d) Patients with recurrent miscarriages or fetal exitus of unknown cause.

The tests should preferably be carried out before pregnancy. However, in those who have not been tested, it is advisable to do so at the beginning of pregnancy, as the result can modify the therapeutic approach. However, it is important to note that certain parameters are subject to changes due to pregnancy:

- **Decrease** during pregnancy: total and free Protein S. Also, the determination of protein C and S and antithrombin activity during treatment with VKA or heparin may show a falsely low value
- **Increases** during pregnancy: resistance to activated protein C
- **Do NOT change** during pregnancy: mutation of factor V and the prothrombin gene and the rest of the determinations of thrombophilia, both congenital and acquired.

7. SPECIAL SITUATIONS

1. Contraception: one of the main cardiovascular risks of hormonal contraception is the increased risk of thrombosis. This increased risk is mainly due to the presence of oestrogens, with little risk attributed to progestogens. However, there are inconclusive reports that third/fourth generation progestogens may increase the risk. History of DVT/PE, acute DVT/PE, established DVT/PE on anticoagulant therapy, history of major surgery with prolonged immobilisation are conditions that restrict the use of hormonal contraception. The different contraceptive method options in patients with a history of DVT/PE are summarised in Table 5.

2. Invasive techniques: invasive techniques are contraindicated during anticoagulant treatment, including punctures of large vessels that are difficult to access, blind organ punctures, biopsies, etc. If necessary, consult the Haemotherapy and Haemostasis Service. During anticoagulant treatment, intramuscular injections in the gluteal area should be avoided, as they can lead to significant haematomas. The most common site of application of drugs administered intramuscularly is in the abdominal area, avoiding the umbilical area, although they can also be applied in other areas such as

the deltoid or anterior aspect of the thigh, applying strong pressure after administration in order to avoid the formation of haematomas.

3. In patients anticoagulated with VKA or heparins, concomitant use of aspirin (unless medically indicated), non-steroidal anti-inflammatory drugs or other drugs that modify platelet functionalism should be avoided due to the increased risk of haemorrhage.

Table 5. Contraceptive methods in patients with a history of DVT/PE

Condition	COCP	CI	PCC/VCC	POC	MPA/ DMPA/ NET-EN	Implants LNG/ETG	IUD-Cu	IUD-LNG
Deep Vein Thrombosis (DVP)/ Pulmonary embolism PE)								
a) Antecedent DVP/PE	4	4	4	2	2	2	1	2
b) Current DVP/PE	4	4	4	3	3	3	1	3
c) Familiar history DVP/PE (first-degree)	2	2	2	1	1	1	1	1
d) Mayor surgery								
(i) Prolonged immobilisation	4	4	4	2	2	2	1	2
(i) NO Prolonged immobilisation	2	2	2	1	1	1	1	1
e) Minor surgery without immobilisation	1	1	1	1	1	1	1	1
Known thrombogenic mutations (factor V Leiden, prothrombin mutation, protein S, protein C and antithrombin deficiencies)	4	4	4	2	2	2	1	2
Superficial venous thrombosis								
a) Varicose veins	1	1	1	1	1	1	1	1
b) Superficial thrombophlebitis	2	2	2	1	1	1	1	1

1 A condition for which there is no restriction on the use of the contraceptive method

2 A condition where the advantages of using the method generally outweigh the theoretical or proven risks.

3 A condition where the theoretical or proven risks generally outweigh the advantages of using the method.

4 A condition that poses an unacceptable health risk if the contraceptive method is used.

COCP: Combined Oral Contraceptives Pills. CI: Contraceptive injection. PCC/VCC: Patch/Vaginal ring combined contraceptive. POC: Progestin-only contraceptive . MPA/DMPA/NET-EN: Medroxyprogesterone acetate/ Depot-Medroxyprogesterone acetate/ Entanato de noretisterona/ Norethisterone enanthate. Implants LNG/ETG: Levonorgestrel y etonogestrel. IUD-Cu: Copper intrauterine device IUD- LNG: Levonorgestrel intrauterine device

8. ANNEX

ANNEX 1. Antenatal risk factors and thromboprophylaxis

THROMBOPROPHYLAXIS DURING PREGNANCY		
HIGH RISK	- Any previous VTE except a single event related to major surgery	LMWH prophylactic dose during pregnancy
	- Recurrent VTE - Treatment with VKA - Antithrombin deficiency and antiphospholypid syndrome	STOP oral anticoagulant LMWH high prophylactic or therapeutic dose during pregnancy
	- High risk thrombophilia without VTE with familiar history of VTE no related (homozygote FVL, AT, PS, PC deficiency) - High risk thromophilia without previous VTE or familiar history of VTE (homozygote FVL, AT, PS, PC deficiency)	LMWH prophylactic dose during pregnancy
INTERMEDIATE RISK	- Hospital admission - Single previous VTE related to major surgery - Medical comorbidities (cancer, heart failure, active systemic lupus, inflammatory bowel disease, inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current intravenous drug addiction) - Any surgical procedure e.g. Appendicectomy - OHSS (first trimester only)	Consider antenatal prophylaxis with LMWH and anti-embolism stocking
LOW RISK	- Obesity (BMI ≥ 30) - Age (>35 años) - Parity ≥ 3 - Smoker - Gross varicose veins - Current pre-eclampsia - Paraplegia - Immobility (≥ 3 days) - Family history of unprovoked or estrogen-provoked VTE in first-degree relative. - Low-risk thrombophilia (FVL heterozygote or prothrombin gen mutation G20210A) - Multiple gestation - IVF/ART - COVID 19 Infection	≥ 4 risk factors: Consider antenatal prophylaxis with LMWH and anti-embolism stocking ≥ 3 risk factors: antenatal prophylaxis **from 28 weeks** with LMWH and anti-embolism stocking
		< 3 risk factors: mobilisation and avoidance of dehydration
	- Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distace travel (> 4 hours)	Consider antenatal prophylaxis with LMWM for as long as the situation persists and according to risk factors

Hospital admission of pregnant women with COVID infection ≤ 4 weeks: LMWH during hospital admission. Discharge: If <4 risk factors LMWH during 10 days. If ≥ 4 risk factors during the rest of gestation.
AFS = antiphospholipid syndrome, ART = assisted reproductive technique, AT = antithrombin, FVL = factor V Leiden, IVF = in vitro fertlisation, LMWH = low molecular weight heparin, OHSS = ovarian hyperestimulation syndrome, PC = protein C, PS = protein S, SLE = Systemic lupus erythematosus, VTE = venous thromboembolism

ANNEX 2. Postpartum risk factors and thromboprophylaxis

POSTPARTUM THROMBOPROPHYLAXIS		
HIGH RISK	- Any previous VTE - Anyone requiring antenatal LMWH - High-risk thrombophilia (homozygote FVL or prothrombin gene mutación G20210A, AT, PS o PC Deficiency) - COVID-19 infection ≤ 4 semanas	Prophylactic LMWH dose at least 6 weeks Patients on oral anticoagulants before pregnancy, consult haematology to restart oral therapy on the 2nd or 3rd day. Anti-embolism stocking
INTERMEDIATE RISK	- Obesity (BMI ≥ 30) - Postpartum haemorrhage > 1 litre or transfusion - Immobility (≥ 3 days) - Stillbirth in this pregnancy - Postpartum fever - Pre-eclampsia + FGR - Readmision or prolonged admision (≥ 3 days) in the puerperium (including terminations of pregnancy and abortions) - Any surgical procedure in the puerperium except immediate repair of the perineum. - Medical comorbidities: cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU - Cesarean during labour - Family history of unprovoked or estrogen-provoked VTE in first-degree relative. - Low-risk thrombophilia (FVL heterozygote or prothrombin gen mutation G20210A)	Prophylactic LMWH dose at least 10 days and Anti-embolism stocking (in case of persistence of risk situation or >3 additional risk factors, consider extending thromboprophylaxis 6 weeks postpartum)
LOW RISK	- Age (>35) - Parity ≥ 3 - Smoker - Elective cesarean section - Gross varicose veins - Paraplegia - Operative delivery - Multiple gestation - Prolonged labour (> 24 hours) - COVID 19 > 4 weeks	≥ 3 risk factors: consider LMWH prophylactic dose for up to 10 days and use of anti-embolism stockings. < 3 risk factors: early mobilisation and avoidance of dehydration

AFS = antiphospholipid syndrome, AT = antithrombin, FVL = factor V Leiden, IVDU = intravenous drug user LMWH = low molecular weight heparin, PC = protein C, PS = protein S, SLE = Systemic lupus erythematosus, VTE = venous thromboembolism

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