2018

Progetto Ematologia Romagna

TROMBOFILIA E GRAVIDANZA: TERAPIA

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Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

✓**Relazioni a convegni**: Daiichi Sankyo, Janssen

TROMBOFILIA E GRAVIDANZA: GESTIONE CLINICA

- Frequenza ed eziopatogenesi del tromboembolismo venoso (TEV)
- Indicazioni a screening trombofilia
- Linee guida su profilassi del TEV
- Linee guida su profilassi antitrombotica nelle complicanze ostetriche

Ministero della Salute

DIPARTIMENTO DELLA QUALITÀ
DIREZIONE GENERALE DELLA PROGRAMMAZIONE SANITARIA, DEI LIVELLI DI ASSISTENZA E DEI PRINCIPI ETICI DI SISTEMA
UFFICIO III

RACCOMANDAZIONE PER LA PREVENZIONE DELLA MORTE MATERNA O MALATTIA GRAVE CORRELATA AL TRAVAGLIO E/O PARTO

Raccomandazione n. 6, Marzo 2008

La versione attuale del presente documento è stata condivisa dal Ministero della Salute e dal Coordinamento delle Regioni e Province Autonome per la Sicurezza dei pazienti.

governo clinico — sicurezza dei pazienti

Le cause più frequenti ed efficacemente prevenibili di morte materna nei paesi occidentali sono rappresentate da (1):

- la malattia tromboembolica
- l'emorragia postpartum
- l'ipertensione –preeclampsia
- la sepsi
- la morte dovuta ad anestesia

Embolia polmonare è la principale causa non ostetrica di mortalità materna**:**
2/100 000 gravidanze
15% di morti materne (prevenibili)

Pregnant women are at an increased risk of VTE: antepartum

0.5-2.2 in 1000 pregnancies ☆

- 5-10 fold increase compared to non-pregnant state
- DVT: 80%, 2/3 occur antepartum

- systematic review:
- event rates for DVT of 21.9 %, 33.7% and 47.6% for the 1st, 2nd, 3rd trimesters, respectively [1]
- recent study: risk might increase exponentially over the duration of the pregnancy [2]
- 12.4% in 1st trimester
- 15.3 % in the 2nd trimester
- 72.3% in the 3rd trimester
- 21-fold increased risk for the last 2 weeks before delivery

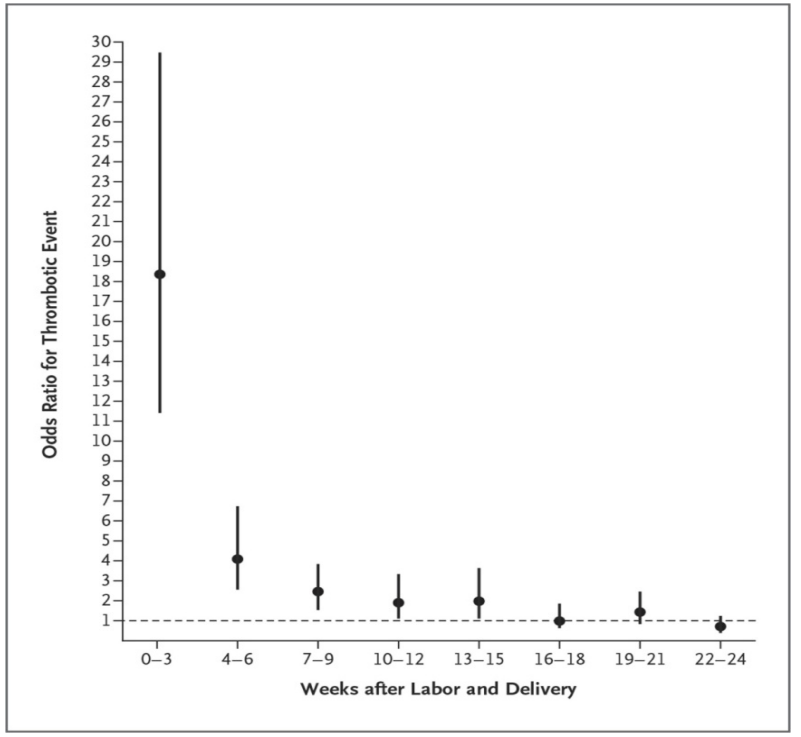
1-Ray JG - Obstet Gynecol Surv 1999; 2-Virkus RA; Thromb Haemost 2011

Pregnant women are at an increased risk of VTE:postpartum

Up to 60% of PE occur 4-6 weeks after delivery

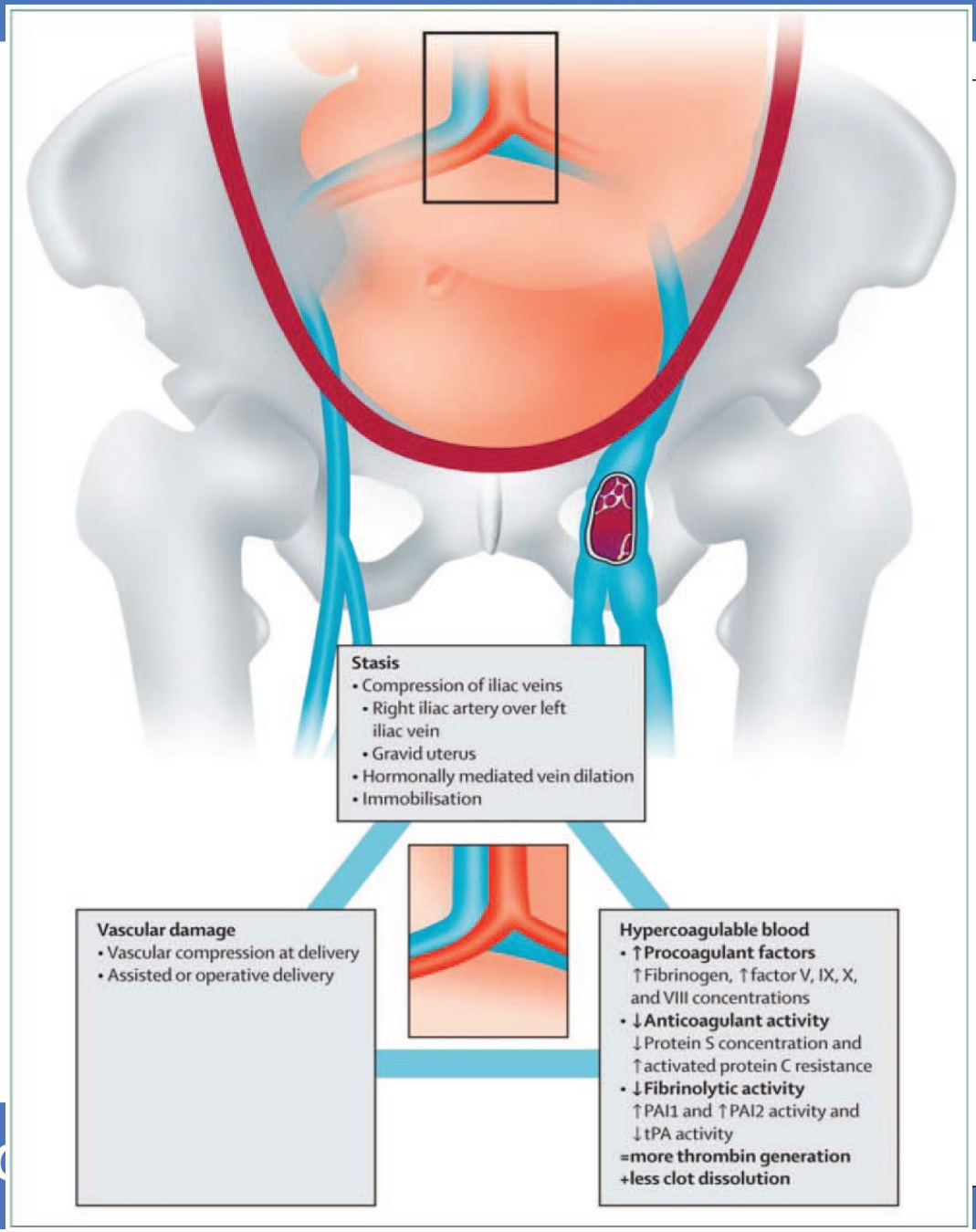
- Daily risk of PE and DVT highest following delivery than antepartum (x9: 1.36 vs 0.15)
- x 10-20-fold, up to 80-fold in the postpartum period.

- high in the 1st postpartum week
- particularly after caesarean section
- decreases afterwards, reaching the non-pregnant level after 6 w
- modest still significantly increased risk (odds ratio [OR] 2.2, 95% CI: 1.5–3.1) for the period from 7–12 w postpartum



Kamel H et al. NEJM,2014

Pregnancy and VTE: pathogenesis



Lancet 2010; 375:500–512

GRAVIDANZA ED IPERCOAGULABILITA'

fattore	gravidanza	Post-partum**
XIII, XII, X, VIII, vWF, VII, fibrinogeno	↑↑	Fibrinogeno aumentato nella 1^ settimana
II, V, IX	↑=	
XI	↓	
TF	=	
AT	=	Aumentata nella 1^ settimana
Proteina C	= ↑	
Proteina S	↓↓	↓↓ fino almeno alla 8^ settimana
TFPI	↑↑	
Plasminogeno, u-PA, t-PA,	↑	
PAI-1, PAI-2	↑↑	Normalizzazione funzionale entro 24-48 ore; PAI-2 rimane nel plasma a lungo
TAFI	=	
α_2-antiplasmina	↑=	

**In genere, si ha normalizzazione completa dopo 3 mesi

Hellgren, 2003

Modalità del parto e rischio di TEV

Modalità del parto	*No. di eventi tromboembolici/ No. di gravidanze*	*Rischio per mille gravidanze (95% intervallo di confidenza)*
Parto vaginale	125 / 556040	0.22 (0.19-0.96)
Taglio cesareo elettivo	23 / 33779	0.68 (0.4-0.96)
Taglio cesareo in urgenza	47 / 55839	0.84 (0.6-1.01)
Tutti i tagli cesarei	70 / 89618	0.78 (0.6-0.96)

RCOG, 1995

VTE AND PREGNANCY: ROLE OF THROMBOPHILIA

Table II. Risk of a first pregnancy-related venous thromboembolism (VTE) in women with hereditary thrombophilia [19, 20]

Thrombophilia	Prevalence, %	Relative risk of VTE, OR (95% CI)	Estimated absolute risk of VTE per 1000 pregnancies*
Factor V Leiden mutation			
Heterozygous	2.0 – 7.0	8.3 (5.4 – 12.7)	8
Homozygous	0.2 – 0.5	34.4 (9.9 – 120.1)	34
Prothrombin G20210A mutation			
Heterozygous	2.0	6.8 (2.5 – 18.8)	7
Homozygous	rare	26.4 (1.2 – 559.3)	26
Factor V Leiden and prothrombin G20210A mutation compound heterozygous	0.18	44 (25 – 79)	44
Antithrombin deficiency†	< 0.1 – 0.6	4.7 (1.3 – 17.0)	5
Protein C deficiency	0.2 – 0.3	4.8 (2.2 – 10.6)	5
Protein S deficiency	< 0.1	3.2 (1.5 – 6.9)	3

Abbr.: VTE: Venous thromboembolism, OR: Odds ratio, CI: Confidence interval. *Assuming a baseline risk of 1 event per 1000 pregnant patients without any known thrombophilia. †Although data are limited, VTE risk is supposed to be substantially higher in antithrombin-deficient pregnant women and can increase up to 20-to 28-fold, depending on the type and extent of antithrombin deficiency [18, 122 – 124].

Linneman, Vasa, 2016

Indicazioni allo screening trombofilia in gravidanza

- Scopo del test: prevenzione primaria del TEV in gravidanza
- opzione molto discussa
- solo studi osservazionali, caso controllo, no RCT
- non chiaro beneficio
- TEV patogenesi multifattoriale: molti altri fattori coinvolti

Connors JM, ***N Engl J Med 2017;377:1177***

Indicazioni allo screening trombofilia in gravidanza

non è suggerito

- nelle donne asintomatiche, gravide o che si accingono ad affrontare una prima gravidanza, in assenza di documentata storia personale o familiare di TEV
(evidenza C)

- nelle donne asintomatiche con storia familiare di complicanze ostetriche (evidenza D)

Rischio tromboembolico in Gravidanza e puerperio SIGO, AOGOI,AGUI, Siset Nov 2014

Indicazioni allo screening trombofilia in gravidanza

E’ suggerito:

nelle donne asintomatiche:

1. con storia familiare di TEV (evidenza D)
2. con storia familiare di trombofilia ereditaria (evidenza C)

nelle donne sintomatiche:

1. con pregresso TEV (evidenza C)
2. con aborti ricorrenti o pregressa MEF (evidenza C)
3. con pregressa pre-eclampsia, HELLP syndrome, abruptio placentae, IUGR (evidenza C).

La ricerca degli anticorpi antifosfolipidi è raccomandata nelle donne con aborto spontaneo ricorrente o MEF (grado 1B) (evidenza B)

LG ACCP 2012 non suggeriscono lo screening di trombofilia ereditaria nelle donne con anamnesi di complicazioni gravidiche di cui al punto 3 (grado 2C)

Rischio tromboembolico in Gravidanza e puerperio
SIGO, AOGOI,AGUI, Siset Nov 2014

Indicazioni allo screening trombofilia in gravidanza

Consider screening for inherited thrombophilias in the following scenarios

A personal history of VTE

Family history

First-degree relative with a history of high-risk inherited thrombophilia

ACOG , 2018

Profilassi primaria del TEV in gravidanza

- Cochrane systematic review (16 RCTS in 2592 women) concluded that available information is insufficient to make firm recommendations for prophylaxis.

- Current clinical guidelines are based on these small trials, additional observational studies and indirect evidence suggesting that LMWH substantially decreases the risk of VTE in a wide variety of clinical settings.
- incomplete agreement between the guidelines as to which patients should receive prophylaxis

Bain et al, Cochrane Database of Systematic Reviews CD001689, 2014
Bates SM, J Thromb Thrombolysis 2016; 41:92–128

PROFILASSI ANTITROMBOTICA IN GRAVIDANZA

Di scelta:

Eparina: **EBPM(da preferire)** ☆

- non attraversano la barriera placentare
- non passano nel latte materno

Weight	Enoxaparin
< 50 kg	20 mg daily
50–90 kg	40 mg daily
91–130 kg	60 mg daily*
131–170 kg	80 mg daily*
> 170 kg	0.6 mg/kg/day*
High prophylactic dose for women weighing 50–90 kg	40 mg 12 hourly

*may be given in 2 divided doses

RCOG 2015

Table 4 Suggested LMWH dosing regimens for prophylaxis against pregnancy-related VTE

Prophylactic LMWH[a]
Dalteparin 5000 units once daily
Tinzaparin 4500 units once daily or 75 units/kg once daily
Enoxaparin 40 mg once daily
Nadroparin 2850 units once daily
Intermediate-dose LMWH[a]
Dalteparin 5000 units twice daily or 10,000 units once daily
Tinzaparin 10,000 units once daily
Enoxaparin 40 mg twice daily or 80 mg once daily
LMWH adjusted to a peak anti-Xa level of 0.2–0.6 units/mL

[a] Higher doses may be used in with increased maternal weight

JTT 2016

PROFILASSI ANTITROMBOTICA IN GRAVIDANZA

Contraindications/cautions to LMWH use	
Known bleeding disorder (e.g. haemophilia, von Willebrand's disease or acquired coagulopathy)	
Active antenatal or postpartum bleeding	
Women considered at increased risk of major haemorrhage (e.g. placenta praevia)	
Thrombocytopenia (platelet count < 75×10^9/l)	
Acute stroke in previous 4 weeks (haemorrhagic or ischaemic)	
Severe renal disease (glomerular filtration rate [GFR] < 30 ml/minute/1.73m^2)	
Severe liver disease (prothrombin time above normal range or known varices)	
Uncontrolled hypertension (blood pressure > 200 mmHg systolic or > 120 mmHg diastolic)	

Clinical and laboratory thresholds are taken from the Department of Health's guidelines based on evidence from the nonpregnant population.[5]

RCOG 2015

PROFILASSI ANTITROMBOTICA IN GRAVIDANZA

8.5 Low-dose aspirin

Aspirin is not recommended for thromboprophylaxis in obstetric patients. D

Fondaparinux should be reserved for women intolerant of heparin compounds. D

Fondaparinux use in pregnancy should be in conjunction with a consultant haematologist with expertise in haemostasis and pregnancy. ✓

RCOG 2015

PROFILASSI PRIMARIA DEL TEV IN GRAVIDANZA

- background incidence of VTE during pregnancy of 1/1,000 deliveries
- the absolute risk of VTE in women without a **prior event or family history** remains low (in the range of 5-12/1,000 deliveries) for most of the inherited thrombophilias, except perhaps for homozygous carriers of the factor V Leiden or the prothrombin mutations where the OR from case-control studies suggest baseline risks of pregnancy-related VTE of > 4%.
- Regardless of the presence of **thrombophilia**, a positive family history of VTE increases the risk for VTE twofold to fourfold.
- Paucity of high quality RCTS

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy Antithrombotic Therapy and Prevention of Thrombosis; 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines Bates at al, CHEST 2012; 141(2)(Suppl):e691S

PROFILASSI PRIMARIA DEL TEV IN GRAVIDANZA

9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).

9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).

9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B).

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy.Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines Bates at al, CHEST 2012; 141(2)(Suppl):e691S–e736S

International Consensus Classification criteria for the antiphospholipid syndrome (APS) (23, 24).

APS is present if one of the following clinical criteria and one of the laboratory criteria are met.

Clinical criteria

1. Vascular thrombosis
2. Pregnancy morbidity
   a. One or more unexplained deaths of morphologically normal fetuses after the 10th week of gestation by ultrasound or direct examination of the fetus.
   b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency.
   c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, or
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or > 99th percentile), on two or more occasions at least 12 weeks apart, or
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions at least 12 weeks apart.

PREGNANCY MORBIDITY 2018	N. pts	Age, median (min-max)	N. pts (%) with positive LAC and increased AntiPHL Ab	N. pts (%) with positive LAC and normal AntiPHL Ab	N. pts (%) with negative LAC and increased AntiPHL Ab	Total
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation	243	36 (21-49)	0	0	0	0
One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: eclampsia or severe pre-eclampsia, placental insufficiency	104	35 (17-49)	0	0	0	0
Three or more consecutive unexplained abortions before the 10th week of gestation, without maternal anatomic or hormonal abnormality, and paternal and maternal chromosomal causes	277	38 (18-50)	1 (0.4)	0	0	1 (0.4)
Two consecutive unexplained abortions before the 10th week of gestation, without maternal anatomic or hormonal abnormality, and paternal and maternal chromosomal causes	440	36 (20-50)	0	2 (0.5)	3 (0.7)	5 (1.1)
Miscellaneous: placental abrurption, placentar infarct, premature delivery, intrauterine growth retardation	599	37 (24-45)	3 (0.5)	0	0	3 (0.5)
Total	1663	36 (17-50)	4 (0.2)	2 (0.1)	3 (0.2)	9 (0.5)

Anticoagulation for VTE prophylaxis

Low-risk thrombophilia without personal VTE history
Antepartum: Surveillance without anticoagulation therapy
Postpartum: Surveillance without anticoagulation therapy or
Postpartum prophylactic anticoagulation therapy
if additional risk factors (e.g., obesity, immobilization, cesarean section**)**

Low-risk thrombophilia plus first-degree relative VTE history
Antepartum: Surveillance without anticoagulation therapy or
Prophylactic LMWH/UFH
Postpartum: Postpartum prophylactic anticoagulation therapy or
Intermediate-dose LMWH/UFH

Low-risk thrombophilia with single episode of VTE
(not receiving long-term anticoagulation therapy)
Antepartum: Prophylactic or intermediate-dose LMWH/UFH
Postpartum: Postpartum prophylactic anticoagulation therapy or
Intermediate-dose LMWH/UFH

ACOG , 2018

Anticoagulation for VTE prophylaxis

High-risk thrombophilia without previous VTE

Antepartum: Prophylactic or intermediate-dose LMWH/UFH

Postpartum : Postpartum prophylactic anticoagulation therapy or Intermediate-dose LMWH/UFH

High-risk thrombophilia with one previous episode of VTE or affected first-degree relative (not receiving long-term anticoagulation therapy)

Antepartum: Prophylactic or Intermediate-dose LMWH/UFH or Adjusted-dose LMWH/UFH

Postpartum:Postpartum prophylactic anticoagulation therapy or Intermediate-dose LMWH/UFH or Adjusted-dose LMWH/UFH for 6 weeks

(therapy level should equal selected antepartum treatment)

Thrombophilia with ≥2 VTE episodes (not receiving long-term anticoagulation)

Antepartum: Intermediate-dose LMWH/UFH or Adjusted-dose LMWH/UFH

Postpartum: Intermediate-dose LMWH/UFH or Adjusted-dose LMWH/UFH for 6 weeks

(therapy level should equal selected antepartum treatment)

Thrombophilia with ≥2 VTE episodes (receiving long-term anticoagulation)

Antepartum: Adjusted-dose LMWH/UFH

Postpartum: Resumption of long-term anticoagulation therapy

Oral route may be considered, depending on therapy duration, breastfeeding and patient preference

ACOG , 2018

Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

Prepregnancy and antenatal risk assessment

What are the risk factors for venous thromboembolism (VTE) in pregnancy and the puerperium and what is the magnitude of risk for these factors?

All women should undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy. C

Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems. C

Risk assessment should be repeated again intrapartum or immediately postpartum. C

Risk factors for pregnancy-associated VTE (RCOG 2015)

Pre-existing risk factors	– Previous venous thromboembolism – Thrombophilia (hereditary or acquired) – Age >35 years old – Obesity (body mass index >30 kg/m²) – Hypertensive disorders of pregnancy – Parity ≥3 – Smoking – Gross varicose veins or symptomatic varicosis – Paralysis or paraplegia – Medical comorbidities, e.g., heart or lung disease, inflammatory bowel disease, inflammatory polyarthropathy, systemic lupus erythematosus, nephrotic syndrome, type I diabetes mellitus with nephropathy, cancer, sickle cell disease
Obstetric risk factors	– Multiple pregnancy – Pre-eclampsia – Caesarean section – Prolonged labour (>24 hours) – Mid-cavity or rotational operative delivery – Severe postpartum haemorrhage (PPH)
Transient or potentially reversible risk factors	- Assisted reproductive technology (ART), in vitro fertilization (IVF) – Ovarian hyperstimulation syndrome (OHSS) (first trimester) – Any surgical procedure in pregnancy or puerperium (e.g., appendectomy, evacuation of retained products of conception [ERPC], postpartum sterilisation) – Hyperemesis, dehydration – Hospital stay or bed rest/immobility ≥3 days – Systemic infection (e.g., pneumonia, pyelonephritis, postpartum wound infection) – Long-distance travel (>4 – 6 hours)

Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

Risk factors for VTE

Pre-existing risk factors	Tick	Score
Previous VTE (except a single event related to major surgery)		4
Previous VTE provoked by major surgery		3
Known high-risk thrombophilia		3
Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user		3
Family history of unprovoked or estrogen-related VTE in first-degree relative		1
Known low-risk thrombophilia (no VTE)		1[a]
Age (> 35 years)		1
Obesity		1 or 2[b]
Parity ≥ 3		1
Smoker		1
Gross varicose veins		1
Obstetric risk factors		
Pre-eclampsia in current pregnancy		1
ART/IVF (antenatal only)		1
Multiple pregnancy		1
Caesarean section in labour		2
Elective caesarean section		1
Mid-cavity or rotational operative delivery		1
Prolonged labour (> 24 hours)		1
PPH (> 1 litre or transfusion)		1
Preterm birth < 37[+0] weeks in current pregnancy		1
Stillbirth in current pregnancy		1
Transient risk factors		
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation		3
Hyperemesis		3
OHSS (first trimester only)		4
Current systemic infection		1
Immobility, dehydration		1
TOTAL		

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission to hospital within the puerperium consider thromboprophylaxis.

For patients with an identified bleeding risk, the balance of risks of bleeding and thrombosis should be discussed in consultation with a haematologist with expertise in thrombosis and bleeding in pregnancy.

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Royal College of Obstetricians & Gynaecologists

Green-top Guideline No. 37a
April 2015

Appendix I: Obstetric thromboprophylaxis risk assessment and managemer

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

Any previous VTE except a single event related to major surgery

→ **HIGH RISK**
Requires antenatal prophylaxis with LMWH
Refer to trust-nominated thrombosis in pregnancy expert/team

- Hospital admission
- Single previous VTE related to major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendicectomy
- OHSS (first trimester only)

→ **INTERMEDIATE RISK**
Consider antenatal prophylaxis with LMWH

- Obesity (BMI > 30 kg/m²)
- Age > 35
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current pre-eclampsia
- Immobility, e.g. paraplegia, PGP
- Family history of unprovoked or estrogen-provoked VTE in first-degree relative
- Low-risk thrombophilia
- Multiple pregnancy
- IVF/ART

→ **Four or more risk factors: prophylaxis from first trimester**

Three risk factors: prophylaxis from 28 weeks

Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel

Fewer than three risk factors

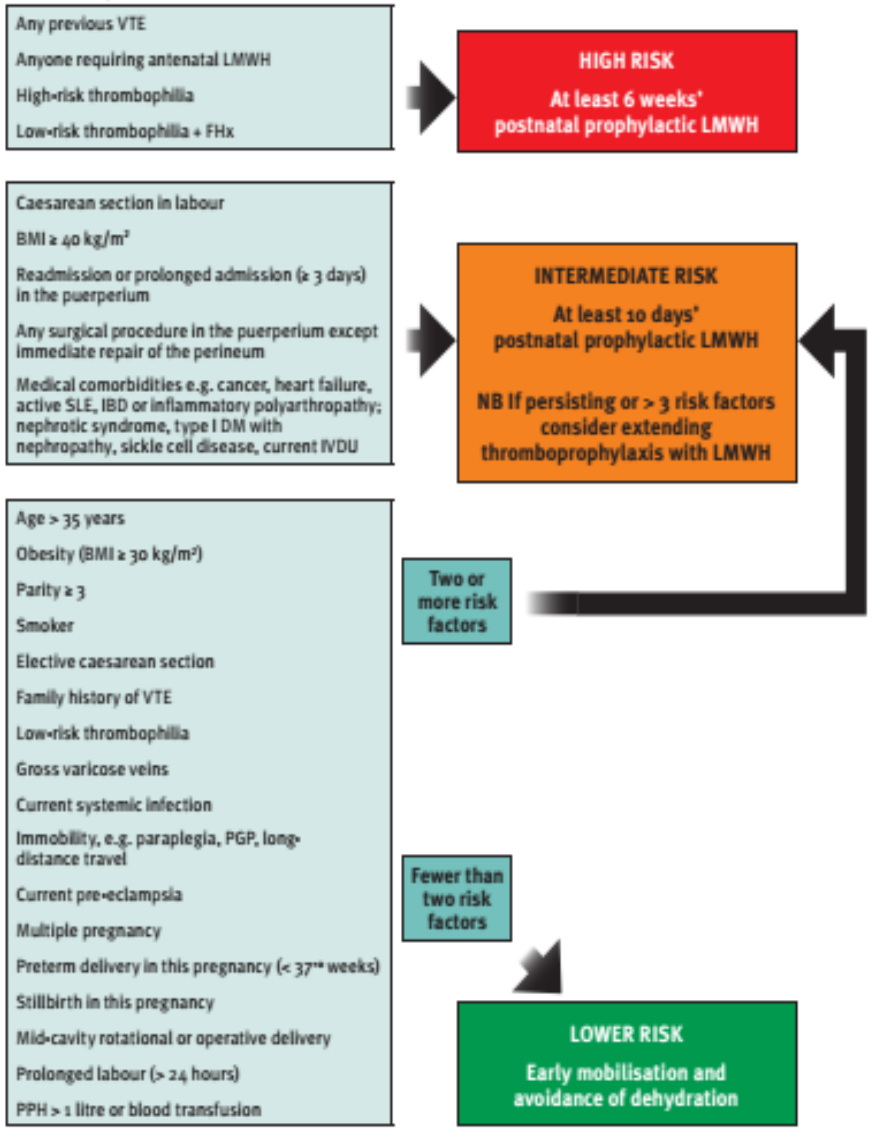
→ **LOWER RISK**
Mobilisation and avoidance of dehydration

Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

Postnatal assessment and management (to be assessed on delivery suite)



7.5 For how long should thromboprophylaxis be continued after delivery?

Risk assessment should be performed in each woman at least once following delivery and before discharge and arrangements made for LMWH prescription and administration (usually by the woman herself) in the community where necessary. ✓

Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women (see Appendix I). C

In women who have additional persistent (lasting more than 10 days postpartum) risk factors, such as prolonged admission, wound infection or surgery in the puerperium, thromboprophylaxis should be extended for up to 6 weeks or until the additional risk factor/s is/are no longer present. D

Cesena, 15 settembre 2018

Results
Characteristics of patients

- 222 women (mean age:34; median:34; range: 19-45) were enrolled.
- Previous VTE was present in 44 (19.8%- DVT: 35)
- Thrombophilia was present in 201 (90.5%):
  - –LAC : 3 (1.5%)
  - –Prot S,C, AT def : 20 (10%)
  - –FV Leiden: 101 (50%- all heterozygotes)
  - –FII : 67 (33% - 1 homozygote)
  - –Double defect/ heterozygosity: 9 (4.5%)
  - –Hyperomocysteinemia: 1 (0.5%)

Results
Characteristics of patients

- Ante-partum prophylaxis was prescribed
- in 61 /171 (35%) women evaluated from 2011 to 2014 according to the SISET guidelines and
- in 22/47 (45%) of women evaluated in 2015 according to RCOG.
- In the former group the RCOG score of VTE risk was applied retrospectively and it was ≥ 3 in 86.7% of subjects.
- Such a score would entail antepartum thromboprophylaxis from the first trimester with a score ≥ 4 or from the 28th week if ≥ 3.

Results

- Compliance with prophylaxis was 92% (200/222).
- Miscarriages occurred in 14 cases (6.3%),
- VTE events in 3 patients (2 DVT and PE) (1.4%; 95% CI: 0-4%) all in the puerperium.
- Bleeding was observed in 6 cases (2.8%; 95% CI:1-6%):
- 4 minor peri-partum bleedings
- 2 major haemorrhages (1 associated with DIC in cesarean section without any ante-partum LMWH and 1 associated with cesarean section with placenta accreta) (0.96% ; 95% CI: 0-3%).
- HIT: 0%

Low-molecular-weight heparin and recurrent placenta mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials, Rodger MA et al, *Lancet* 2016; 388: 2629–41

	Trial enrolment	Participants randomly assigned in original trial	Participants eligible for IPDMA by qualifying previous complications*	LMWH intervention and control
TIPPS[14] 2014	Multinational: 21 sites in Canada, US, Australia, and the UK	292 with thrombophilia and previous high-risk criteria	113 total 48 pre-eclampsia 47 SGA 18 placental abruption 36 ≥2 fetal losses after 12 weeks' GA 62 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU to 20 weeks' GA then 10 000 IU to 36 weeks' GA Control: no dalteparin Aspirin use permitted
FRUIT[15] 2012	Multinational: 12 sites in the Netherlands, Sweden, and Australia	139 with heritable thrombophilia and previous early-onset pre-eclampsia or SGA <10th percentile (or both)	136 total 106 pre-eclampsia 47 SGA 11 placental abruption 41 ≥2 fetal losses after 12 weeks' GA 43 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU plus aspirin Control: aspirin alone
HAPPY[16] 2012	Multicentre: 8 sites in Italy	135 with previous pre-eclampsia, loss >15 weeks' GA, SGA <10th percentile, or placental abruption	124 total 49 pre-eclampsia 53 SGA 20 placental abruption 41 ≥2 fetal losses after 12 weeks' GA 41 ≥1 fetal loss after 16 weeks' GA	Treatment: nadroparin 3800 IU Control: no nadroparin Aspirin use discouraged
HABENOX[17] 2011	Multinational: 4 sites in Finland, Sweden, and the Netherlands	207 with recurrent early or late miscarriage	37 total 0 pre-eclampsia 1 SGA 4 placental abruption 14 ≥2 fetal losses after 12 weeks' GA 29 ≥1 fetal loss after 16 weeks' GA	Treatment 1: enoxaparin 40 mg plus placebo Treatment 2: enoxaparin 40 mg plus aspirin Control: aspirin alone
NOH-PE[18] 2011	Single centre in France	224 with previous severe pre-eclampsia	224 total 224 pre-eclampsia 58 SGA	Treatment: enoxaparin 4000 IU plus aspirin Control: aspirin alone
NOH-AP[19] 2010	Single centre in France	160 with previous placental abruption	160 total 160 placental abruption 71 pre-eclampsia 44 SGA	Treatment: enoxaparin 4000 IU Control: no enoxaparin Aspirin use if clinically indicated
ALIFE[20] 2010	Multicentre: 8 sites in the Netherlands	364 (299 pregnant) with recurrent pregnancy loss	38 total 4 pre-eclampsia 5 SGA 3 placental abruption 32 ≥2 fetal losses after 12 weeks' GA 29 ≥1 fetal loss after 16 weeks' GA	Treatment: nadroparin 2850 IU plus aspirin Control 1: aspirin alone Control 2: placebo
Rey[21] 2009	Multicentre: 6 sites in Canada	116 with previous early pre-eclampsia, placental abruption, SGA<5th percentile, and pregnancy loss >12 weeks' GA	113 total 93 pre-eclampsia 62 SGA 36 placental abruption 69 ≥2 fetal losses after 12 weeks' GA 66 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU Control: no dalteparin Aspirin use permitted

LMWH=low-molecular-weight heparin. SGA=small for gestational age. GA=gestational age. Loss=pregnancy loss. *Participants might have had a history of more than one qualifying placenta-mediated pregnancy complication.

Table 1: Trials included in the individual patient data meta-analysis (IPDMA)

pre-eclampsia, placental abruption,
birth of an SGA neonate [<10th percentile],
pregnancy loss after 16 weeks' gestation, or
two losses after 12 weeks' gestation

8 trials:
480 women on LMWH vs
483 women no LMWH;
42% had thrombophilia

14% vs 21% ; NS

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Five Things Physicians and Patients Should Question

1 Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption.

Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies and beta 2 glycoprotein antibodies.

Screening is not recommended for the following

Personal history of

Fetal loss

Abruption

Preeclampsia

Fetal growth restriction

Note: Consider testing for acquired antiphospholipid syndrome antibodies in women with recurrent pregnancy loss or stillbirth

•ACOG states "There is insufficient evidence to recommend
•anticoagulation as an intervention to prevent adverse
•pregnancy outcomes among women
•with inherited thrombophilias"

ACOG,2018