Venous Thrombo-Embolism (VTE) and Pregnancy: Today's Challenges

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Key Points

- Woman are at increased risk for VTE
- Risk is increased regardless of age
- Pregnant women are especially at risk
- Identify high-risk patients
- Choose treatment option

Women are at increased risk of VTE

- Worldwide, 78,000 pregnant women die of VTE every year
- In industrialized countries, the share of VTE in direct maternal deaths is 13.8%.

Say L. et al., Global causes of maternal death: a WHO systematic analysis: Lancet Glob Health. 2014 Jun;2(6):e323-33.

VTE risk is increased at any age

Crosignani PG et al., Venous thromboembolism in woman : a specific reprdoductive health risk. HumUpd, Vol 19, No.5 pp.471-482

VTE Signs & symptoms may be difficult to recognize

Many occur in other symptoms and disorders

DVT is often asymptomatic

PE signs and symptoms overlap with other disorders

DVT in pregnacy is difficult to diagnose

Challenges : identify the specific signs & symptoms?

Crosignani PG et al., Venous thromboembolism in woman : a specific reprdoductive health risk. HumUpd, Vol 19, No.5 pp.471-482

VTE & Pregnancy: Antepartum and postpartum risk factors

Thrombophilia[22]	51·8 (38·7–69·2)*
Previous VTE[22]	24·8 (17·1–36·0)†
Family history of VTE[23]	3·9‡
Superficial venous thrombosis[24]	10·0 (1·3–78·1)
BMI more than 25 kg/m²§[25]	1·8 (1·3–2·4)
Antepartum immobilisation[25]	7·7 (3·2–19·0)¶
BMI more than 25 kg/m²§ and antepartum immobilisation[25]	62·3 (11·5–337·6)
Assisted reproduction	4·3 (2·0–9·4)
Smoking	2·1 (1·3–3·4)

Haemorrhage (without surgery)	4·1 (2·3–7·3)
Haemorrhage (with surgery)	12·1 (3·9–36·9)
Infection (vaginal)	20·2 (6·4–63·5)
Infection (caesarean)	6·2 (2·4–26·3)
IUGR	3·8 (1·4–10·2)
Pre-eclampsia	3·1 (1·8–5·3)‖
Pre-eclampsia and IUGR	5·8 (2·1–16·0)
Emergency caesarean delivery	2·7 (1·8–4·1)**
Caesarean delivery[22]	2·1 (1·8–2·4)
Caesarean delivery[25]	1·3 (0·7–2·2)
Age[22]	2·1 (2·0–2·3)
Parity[25]	1·7 (1·2–2·4)

PREGNANCY 5x

VTE=venous thromboembolism. BMI=body-mass index. IUGR=intrauterine growth restriction.
*Risk varies by type of thrombophilia.8,26,27 †Data accord with results of another study.23 ‡95%

PERPUERIUM 60x

Bourjeily G et al., Pulmonary embolism in pregnancy. Lancet. 2010 Feb 6;375(9713):500-12.

VTE Prophylaxis & Pregnancy: RCOG Guidelines

“A formal VTE risk assessment with numerical scoring for all pregnant and postpartum women is recommended.”

RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015..

VTE Risk Score: RCOG (early pregnancy)

Preexisting risk factors	**Previous VTE (except 1 event associated with a major intervention)**	**4**
	- Previous VTE due to major intervention	**3**
	- High risk of known thrombophilia (e. g. homozygous Leiden factor V)	**3**
	- Comorbidities/internal conditions (e.g., cancer, heart failure, systemic lupus erythematosus)	**3**
	- Positive family history for VTE (first degree parents)	**1**
	- Low risk of known thrombophilia (e. g. heterozygous Leiden factor V)	**1**
	- Age > 35 years	**1**
	- BMI ≥ 30 kg/m2	**1**
	- BMI ≥ 40 kg/m2	**2**
	- Parity ≥ 3 3	**1**
	- Smoking	**1**
	- Pronounced varicose veins	**1**
Obstetrical risk factors	- Preeclampsia in current pregnancy	1
	- Assisted reproduction/in vitro fertilization	1
	- Multiple pregnancy	1
	- Secondary Caesarean section	2
	- Elective Caesarean section	1
	- Surgical vaginal delivery of the central pelvis	1
	- Prolonged delivery (> 24 hours)	1
	- Hemorrhage of delivery (blood loss > 1 l or blood transfusion)	1
	- Premature delivery < 37th SG in current pregnancy	1
	- Stillborn child born during current pregnancy	1
Transient risk factors	Any surgical intervention during pregnancy or after childbirth with the exception of taking immediate loading of perineal lesions (e. g. appendicectomy, postpartum sterilization)	3
	- Hyperemesis gravidarum	3
	- Ovarian hyperstimulation syndrome (only during the 1st trimester)	4
	- Systemic infection during pregnancy	1
	- Immobilization, dehydration	1

Total score

RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015.

Patient case: Lucie

- **Pregnant in the first trimester, 37 years old** 1
- **Family history of VTE (mother)** 1
- **Inflammatory bowel syndrome** 3

VTE Risk Score: RCOG (post-partum)

- any previous VTE
- all pregnant women with antenatal medicinal VTE prophylaxis
- High-risk thrombophilia (hereditary defects, e.g. antithrombin deficiency, combined thrombophilic defects, homozygous factor-
- V Leiden or prothrombin mutation)
- Low-risk thrombophilia + positive family history

→ **VTE risk HIGH**
Postnatal NMH in prophylactic dosage for at least 6 weeks

- secondary section
- BMI ≥ 40 kg/m2
- in case of prolonged (≥ 3 days) or renewed hospital stay
- any surgical intervention (except episiotomy, treatment of injuries to the perineum)
- comorbidity e.g. cancer, heart failure, active lupus erythematosus, nephrotic syndrome, diabetes mellitus type I with nephropathy, inflammatory bowel disease, sickle cell anemia, current intravenous drug dependence

→ **VTE risk MEDIUM**
Postnatal NMH in prophylactic dosage for min. 10 days

- Age > 35 years
- BMI ≥ 30 kg/m2 Parity ≥ 3
- Smoking elective section
- positive family history
- Low-risk thrombophilia (e.g. homozygous factor V Leiden or prothrombin mutation)
- pronounced varicosis
- current systemic infection
- Immobility e.g. paraplegia, long-distance travel
- Preeclampsia in current pregnancy
- multiple pregnancy
- Premature birth < 37. SSW in current pregnancy
- stillbirth in current pregnancy
- vaginal-operative delivery from the middle of the pelvis
- protracted course of birth (> 24 hours)
- postpartum bleeding > 1 liter or blood transfusion

≥2 Risk factors → **VTE risk MEDIUM**
Postnatal NMH in prophylactic dosage for min. 10 days

<2 Risk factors → **VTE risk LOW**
Early mobilisation and prevention
Dehydration

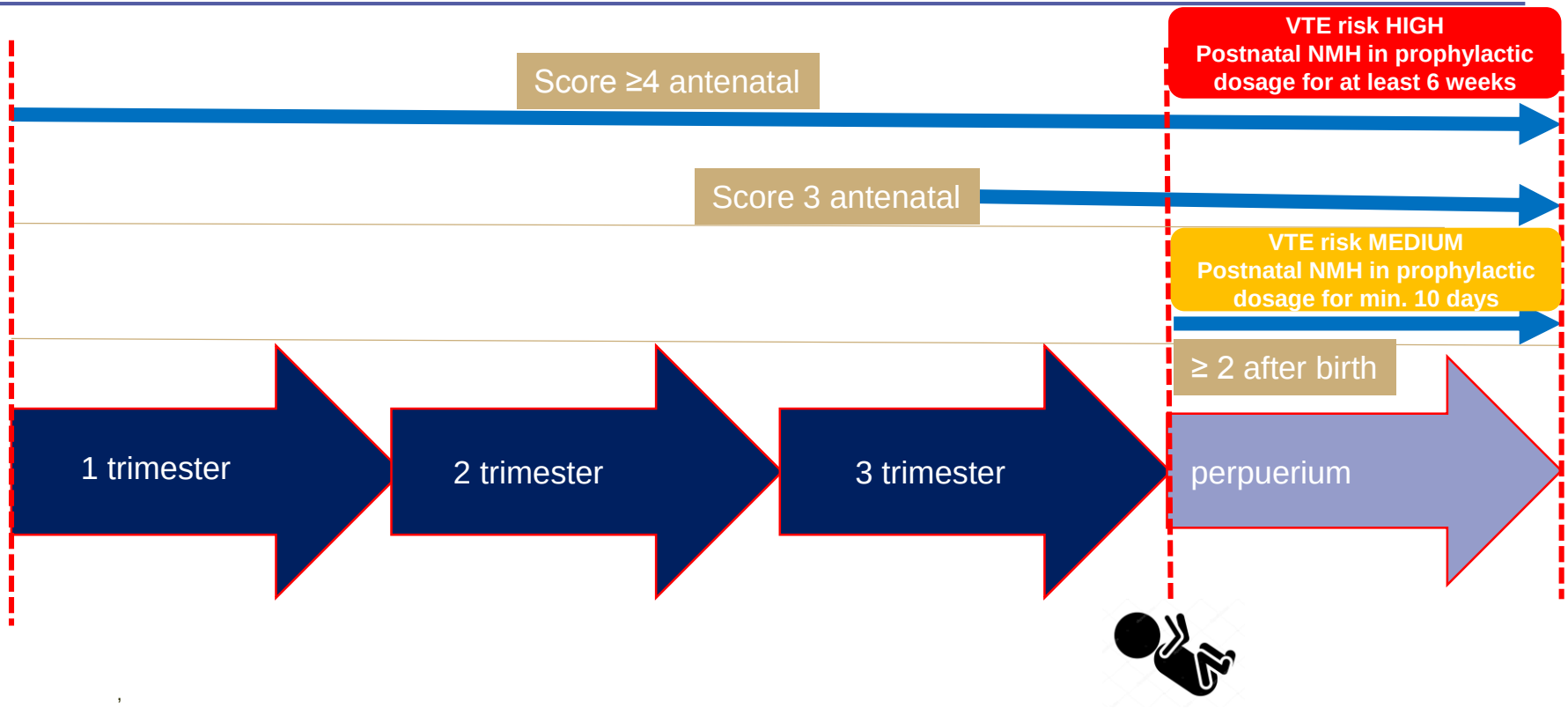
Total Number of Risk factors

RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015. Kevane B. et al., Risk factors for pregnancy-associated venous thromboembolism: a review: J Perinat Med. 2014 Jul;42(4):417-2. Chauleur C. et al., Use of the Delphi method to facilitate antithrombotics prescription during pregnancy: Thromb Res. 2010 Aug;126(2):88-92.

Patient case: Anne

- **40 years old** 1
- **Smoker** 1
- **Premature birth** 1

RCOG Score, Risk Factors, and prophylactic treatment



RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015. Kevane B. et al., Risk factors for pregnancy-associated venous thromboembolism: a review: J Perinat Med. 2014 Jul;42(4):417-2. Chauleur C. et al., Use of the Delphi method to facilitate antithrombotics prescription during pregnancy: Thromb Res. 2010 Aug;126(2):88-92.

VTE Prophylaxis: treatment options

Molecule	Pregnancy	Breastfeeding
LMWHs	✓	✓
UFH	✓	✓
ASA	Not recommended	✓
Fondaparinux	(✓)	Not recommended
Vit K antagonists	✗	✓
Direct Oral Anticoagulants	✗	✗

Not RECOMMENDED in PREGNANCY !!!!
VIT K antagonists
Direct oral anticoagulants

Modified after Scheres et al., Blood Rev. 2018 Aug 6. pii: S0268-960X(18)30020-1. RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015..
Disclaimer: Overall, the studies suggest that there is no evidence of an increased risk of bleeding, thrombopenia or osteoporosis in pregnant women compared to non-pregnant women.
There is limited experience to date with the use of enoxaparin in breastfeeding. Many drugs enter breast milk, but caution is advised against breastfeeding. – for more details please consult www.swissmedicinfo.ch

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Antenatal and postnatal prophylactic dose of LMWH

- Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/
- Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin
- Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin
- Weight 131–170 kg = 80 mg enoxaparin/10 000 units dalteparin
- Weight > 170 kg = 0.6 mg/kg/day enoxaparin/ 75 u/kg/day dalteparin

RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015..

Inherited thrombophilia and RR of VTE

Table III Coagulation abnormalities causing inherited thrombophilia and associated RR of VTE in family studies (Vossen *et al.*, 2004, adapted).

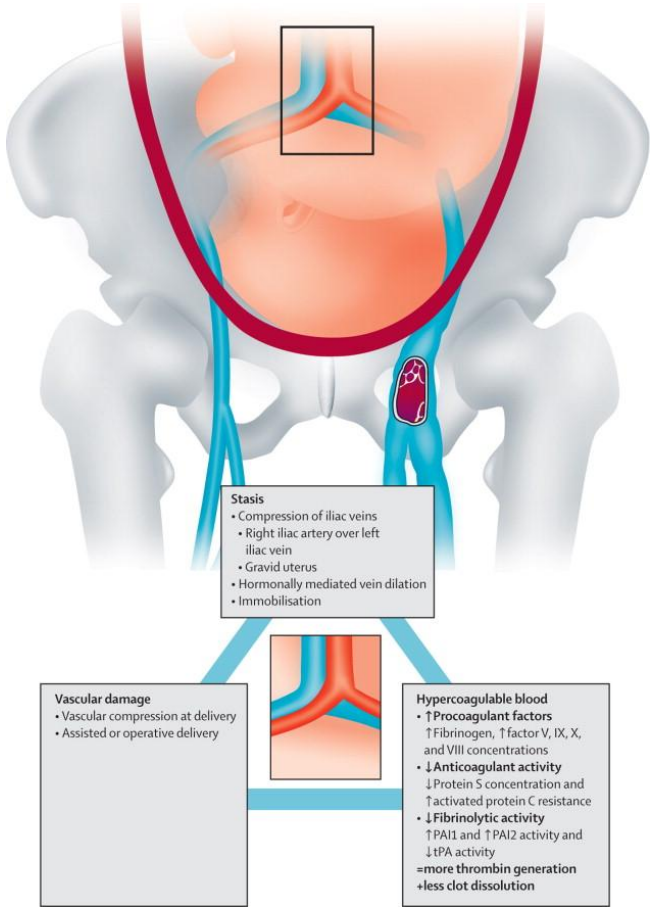
Causes	Prevalence (%)	Relative risk of first venous thrombosis
Antithrombin deficiency	0.02	5–10
Protein C deficiency	0.2	4–6.5
Protein S deficiency	0.03–0.13	1–10
Factor V Leiden	3.0–7.0	3–5
Prothrombin G20210A	0.7–4.0	2–3
High factor VIII	10	5
High factor IX	10	2
High factor XI	10	2

VTE, venous thromboembolsim.

Virchrow’s triad in pregnancy

- VTE in pregnant women 5–12 events/10 000 pregnancies*
- Risk similar in all 3 Semesters
- Incidence DVT 3x > PE
- 85% Left leg – compression of iliac vein

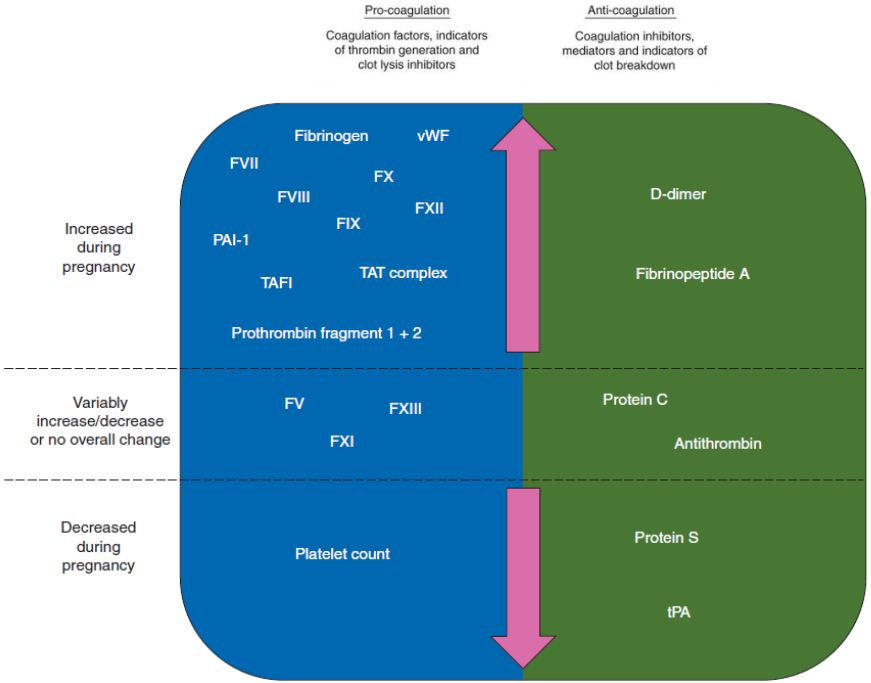
Perpuerium (incidence) 3–7 events/ 10 000 deliveries
Risk - 15–35 x > age-matched controls



* Antenatally -from conception to delivery

Bourjeily G et al., Pulmonary embolism in pregnancy. Lancet. 2010 Feb 6;375(9713):500-12.

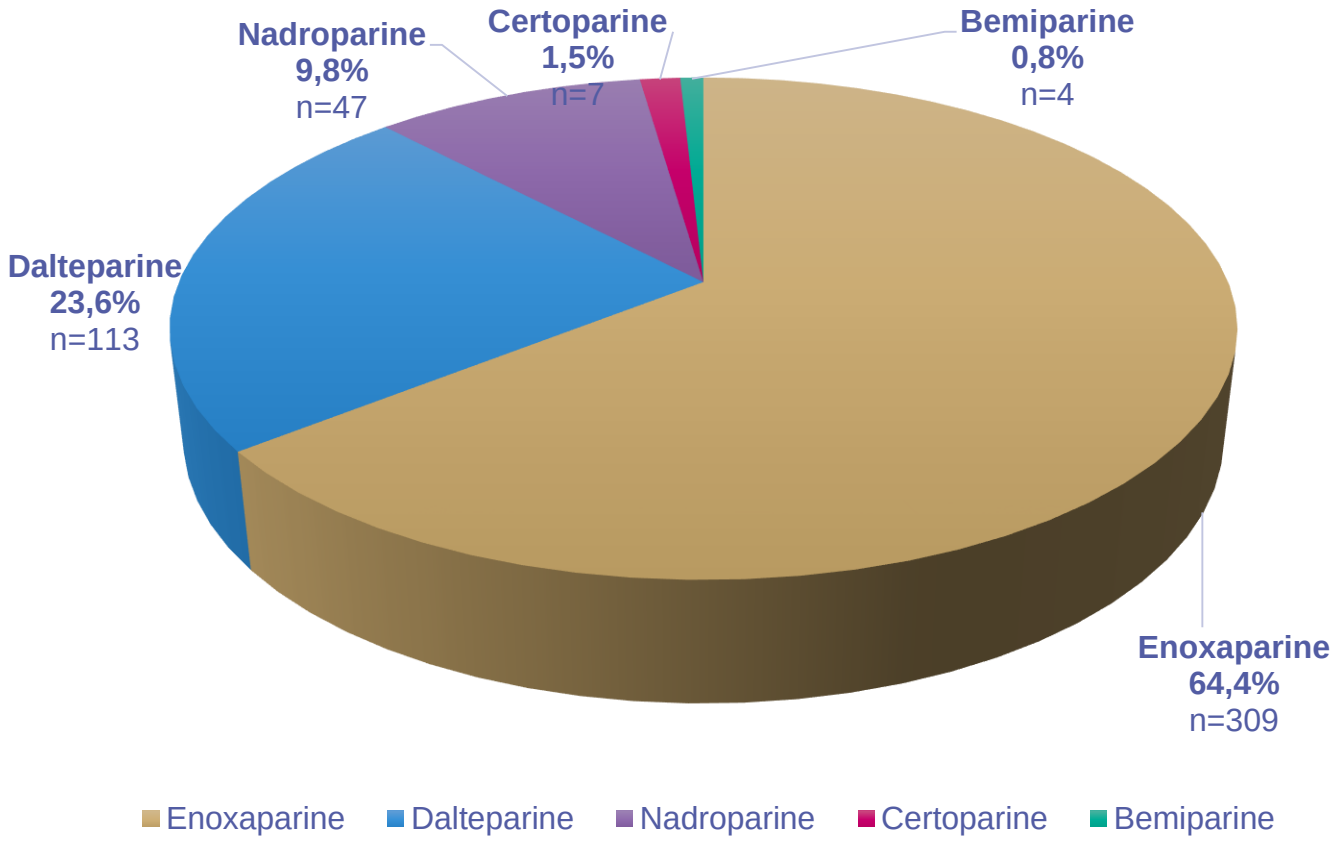
Changes in homeostasis during pregnancy



Changes in haemostatic variables observed during normal, healthy pregnancy. The overall increase in pro-coagulant factors results in a typically hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative of the precise level of increase or decrease. FV, Factor V; FVII, Factor VII; FVIII, Factor VIII; FIX, Factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; FXIII, Factor XIII; PAI-1, plasminogen activator inhibitor 1; TAFI, thrombin activatible fibrinolysis inhibitor; TAT complex, thrombin–antithrombin complex; vWF, von Willebrand factor.

Solomon C et al., Haemostatic monitoring during postpartum haemorrhage and implications for management. British Journal of Anaesthesia 109 (6): 851–63 (2012)

Publications



Percentage distribution of the data published up to 2016 and recorded in a systematic evaluation NMH applications in pregnancy

Risk evaluation – after VTE and/other thrombophilia- RCOG

VTE-Risk		Recommendation
Very High Risk	Previous VTE with oral long-term anticoagulation antithrombin deficiency Antiphospholipid Syndrome with Previous VTE	antenatal high dosed NMH and min. 6 weeks postpartum or until reinstatement with oral Anticoagulants recommended These women need care from a Experts in Haemostasis / Pregnancy
High Risk	any preceding VTE (except one VTE associated with major surgery)	antenatal and 6 weeks postnatal NMH in prophylactic dosage recommended
Middle Risk	asymptomatic high-risk thrombophilia antithrombin Protein C or S deficiency combined thrombophilic defects (incl. homozygous Factor V Leiden, homozygous Prothrombin mutation, compound (combined) heterozygote) a previous VTE associated with a larger Operation without thrombophilia, positive Family anamnesis or other risk factors	refer to local experts antenatal NMH consider 6 weeks postpartum NMH in prophylactic dosage recommended antenatal NMH consider (not routinely recommended) from 28th SSW to 6 weeks postpartum NMH recommended in prophylactic dosage
Low Risk	asymptomatic low-risk thrombophilia (heterozygous factor V Leiden, prothrombin mutation or antiphospholipid syndrome)	Consider as a risk factor in the scoring system postpartum NMH in prophylactic dosage for 10 days or 6 weeks, depending on the Risk profile recommended

RCOG Green-top Guideline No. 37a, Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists: April 2015. Kevane B. et al., Risk factors for pregnancy-associated venous thromboembolism: a review: J Perinat Med. 2014 Jul;42(4):417-2. Chauleur C. et al., Use of the Delphi method to facilitate antithrombotics prescription during pregnancy: Thromb Res. 2010 Aug;126(2):88-92.

Contraception, obesity and smoking

Table IV RRs of deep venous thrombosis in obese women according to age categories (Stein *et al.*, 2005, adapted).

Obese versus non-obese women		
Age group	**RR**	**95% CI**
<40	5.20	5.15–5.25
40–49	2.13	2.11–2.15
50–59	1.67	1.65–1.68
60–69	1.88	1.87–1.90
70–79	1.89	1.87–1.91
≥80	2.16	2.12–2.20
All ages	2.50	2.49–2.51

VTE, venous thromboembolsim.

- Increased risk is related to the dose of estrogen and it is also influenced by the type of progestogen.
- Second generation of progestogens – levonorgstrel (LNG) and norethisterone are safer.
- Non-oral also associated with an increased risk of VTE (patch 7,9x and vaginal ring 6.5x)
- POC only – progesteron only contraception – considered safe
- IUD also but cardiovascular risk not completely assesed

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