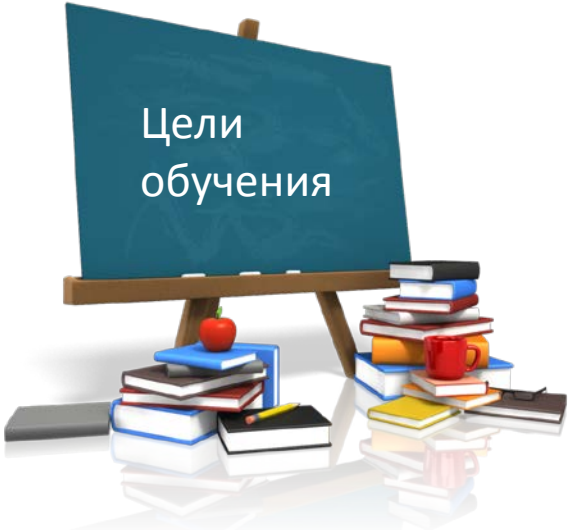
Съезд Congress

5-7 сентября 2018 / Санкт-Петербург
September 5-7, 2018 / St. Petersburg

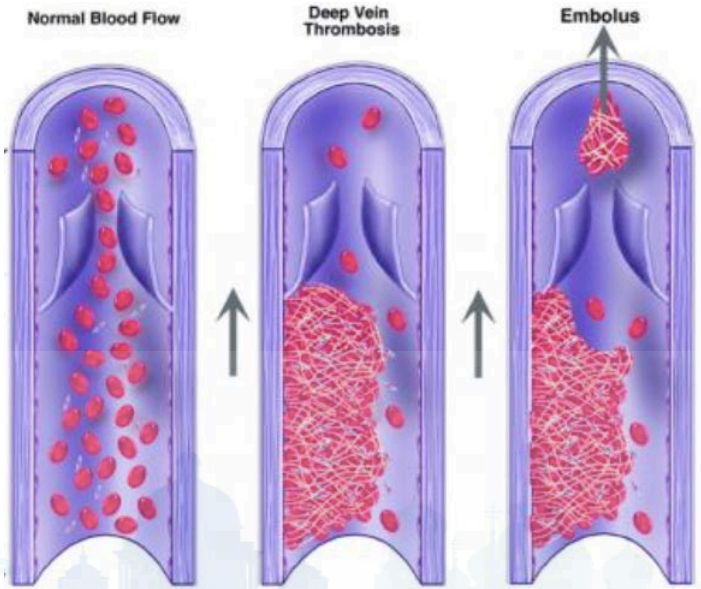
Thromboembolic disease in pregnancy

Nuala Lucas
London North West University Healthcare



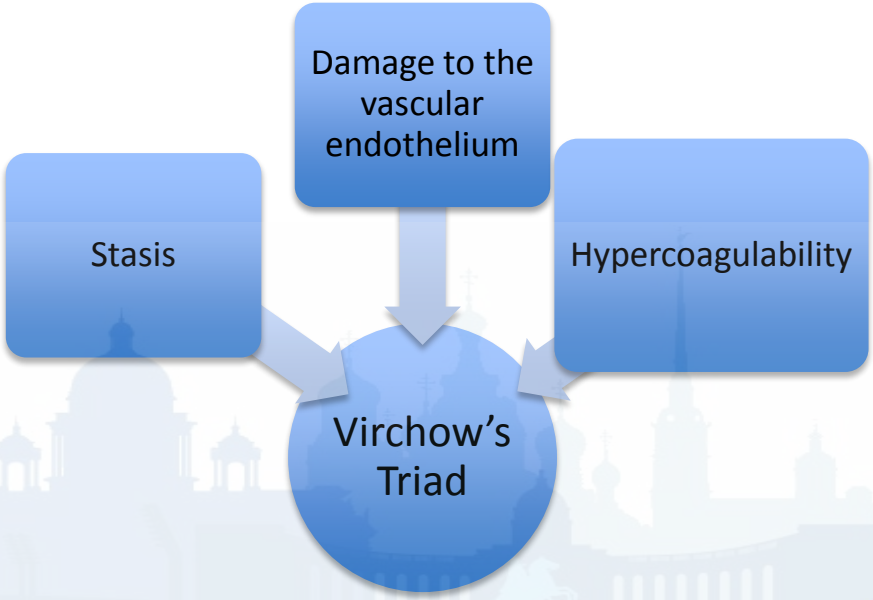
- Pathophysiology of thromboembolic disease in pregnancy
- How to prevent thromboembolic disease
- How to treat thromboembolic disease
- Some of the problems associated with thromboprophylaxis

Pathophysiology of deep vein thrombosis

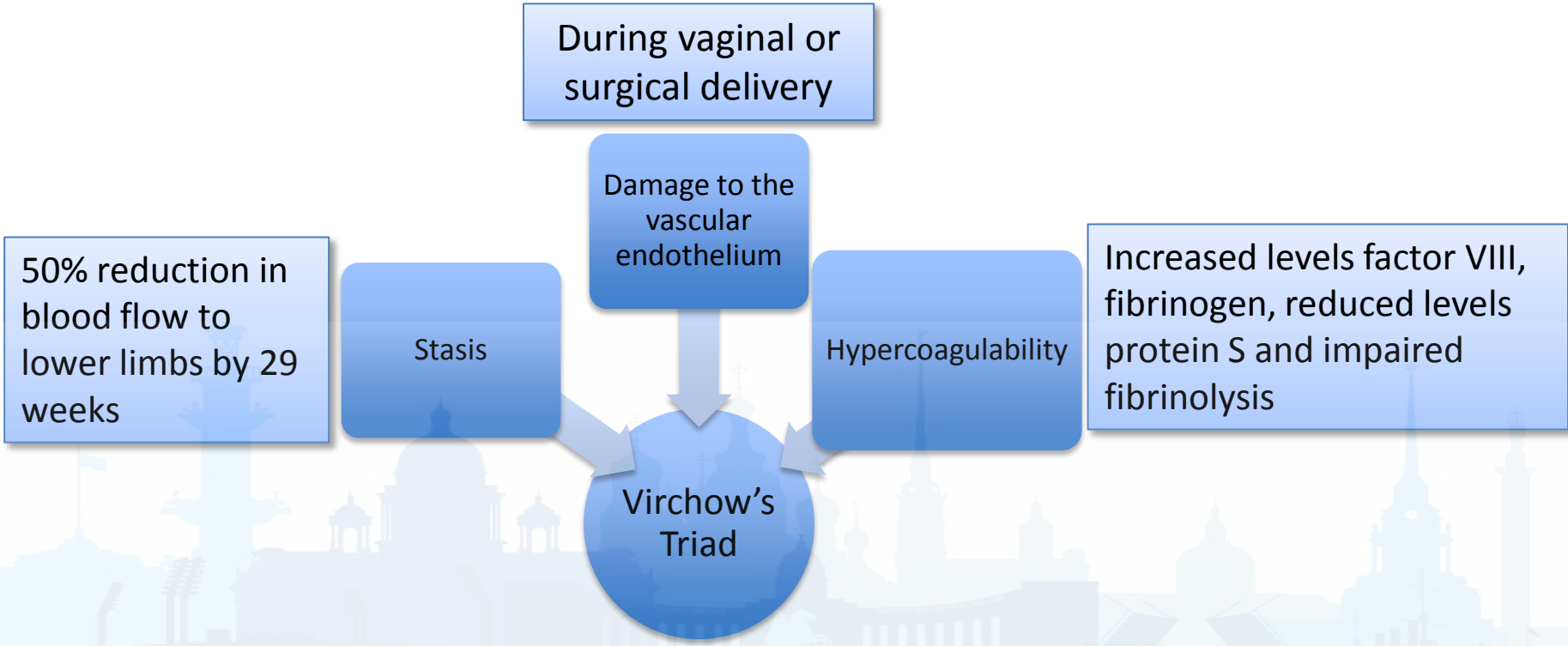


3 questions
Why?
Where?
When?

Why are obstetric patients at risk?



Why are obstetric patients at risk?



Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a

April 2015

The American College of Obstetricians and Gynecologists

WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 196

(Replaces Practice Bulletin Number 123, August 2011)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics in collaboration with Andra James, MD, MPH; Meredith Birsner, MD; and Anjali Kaimal, MD, MAS.

Thromboembolism in Pregnancy

Risk factors in pregnancy

Table 1. Risk factors for venous thromboembolism in pregnancy and the puerperium

See also Appendix I and Appendix II		
Pre-existing	Previous VTE	
	Thrombophilia	*Heritable* Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene mutation
		Acquired Antiphospholipid antibodies Persistent lupus anticoagulant and/or persistent moderate/high titre anticardiolipin antibodies and/or β_2-glycoprotein 1 antibodies
	Medical comorbidities e.g. cancer; heart failure; active SLE, inflammatory polyarthropathy or IBD; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease;[49] current intravenous drug user	
	Age > 35 years	
	Obesity (BMI ≥ 30 kg/m^2) either prepregnancy or in early pregnancy	
	Parity ≥ 3 (a woman becomes para 3 after her third delivery)	
	Smoking	
	Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)	
	Paraplegia	
Obstetric risk factors	Multiple pregnancy Current pre-eclampsia	
	Caesarean section Prolonged labour (> 24 hours) Mid-cavity or rotational operative delivery Stillbirth Preterm birth Postpartum haemorrhage (> 1 litre/requiring transfusion)	
New onset/transient *These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve and therefore what is important is an ongoing individual risk assessment*	Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation Bone fracture	
	Hyperemesis, dehydration	
	Ovarian hyperstimulation syndrome (first trimester only)	Assisted reproductive technology (ART), in vitro fertilisation (IVF)
	Admission or immobility (≥ 3 days' bed rest)	e.g. pelvic girdle pain restricting mobility
	Current systemic infection (requiring intravenous antibiotics or admission to hospital)	e.g. pneumonia, pyelonephritis, postpartum wound infection
	Long-distance travel (> 4 hours)	

Additional risk factors

Maternal

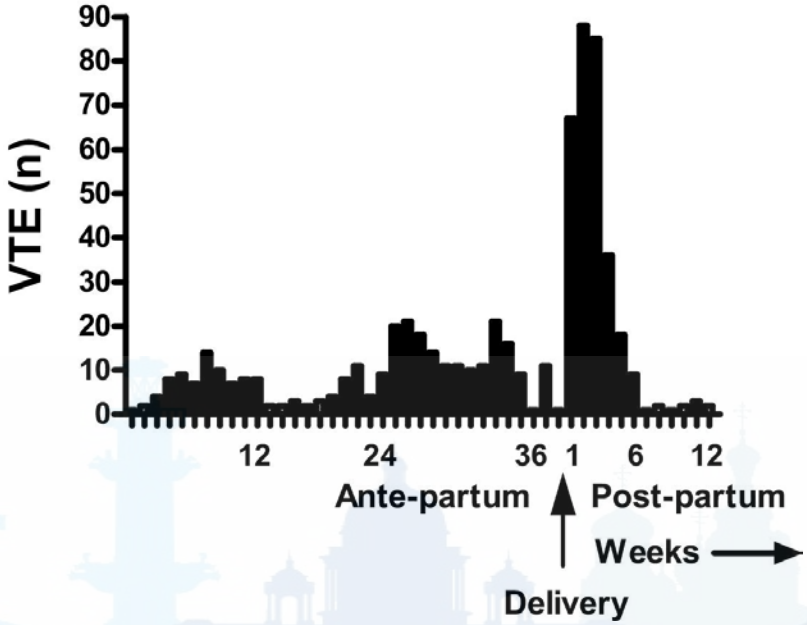
- Previous history of thromboembolism
  - Pregnancy increases risk of recurrence 3-4 x
  - 15-25% of pregnancy related thrombosis are recurrent events
- Obesity
- Age
- Parity

Pregnancy related

- Hyperemesis
- Pre-eclampsia
- Morbidity
  - Haemorrhage
  - Sepsis
- Mode of delivery

Increasing risk with mode of delivery

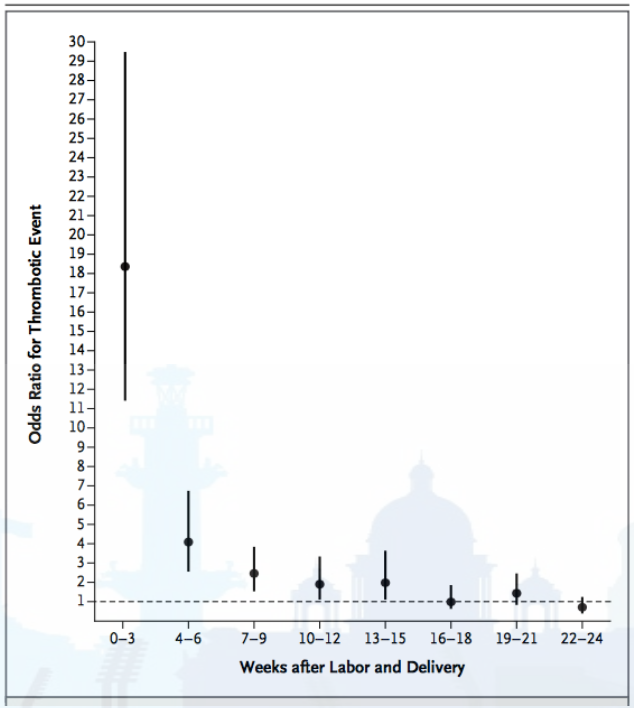
When does venous thromboembolism in pregnancy and the postnatal period occur?



Distribution of venous thromboembolism in pregnancy and postnatal period

Jacobsen, Obstet Gynecol, 2008

How long after delivery does risk persist for?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of a Thrombotic Event after the 6-Week Postpartum Period

Hooman Kamel, M.D., Babak B. Navi, M.D., Nandita Sriram, B.S., Dominic A. Hovsepian, B.S., Richard B. Devereux, M.D., and Mitchell S.V. Elkind, M.D.

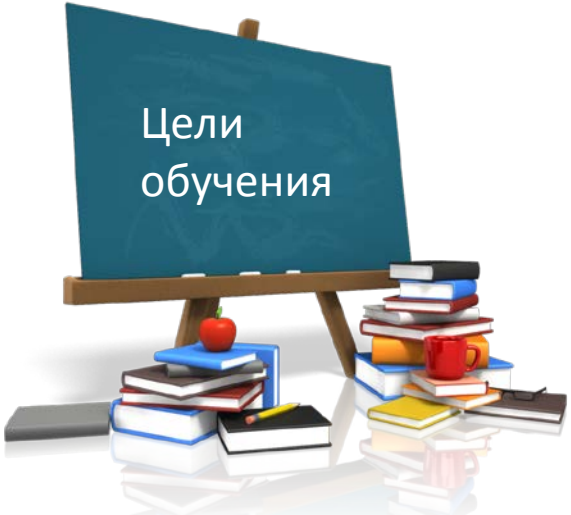
'…elevated risk of thrombosis persisted until at least 12 weeks after delivery. However, the absolute increase in risk beyond 6 weeks after delivery was low.'

Venous thromboembolism in pregnancy - where does it occur?

- 70-90% of DVT on left side (*55% outside pregnancy*)
  - ?physical effect - gravid uterus compressing left iliac vein as it crosses right iliac artery

- >70% proximal ileofemoral vessels (9% *outside pregnancy)*

- >70% post-phlebitic syndrome

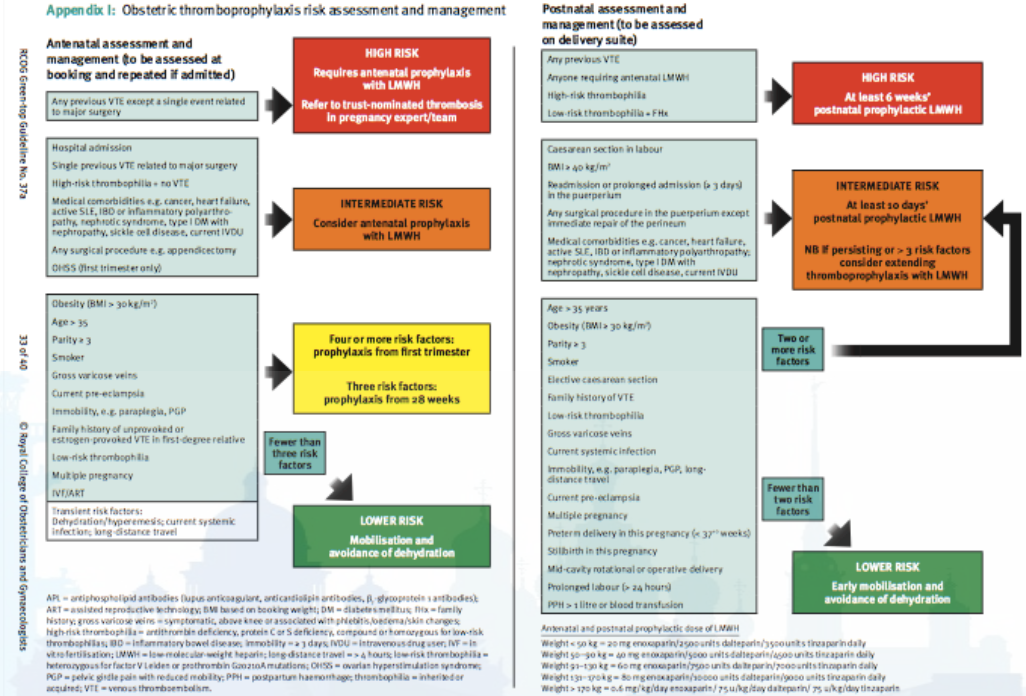


- Pathophysiology of thromboembolic disease in pregnancy
- How to prevent thromboembolic disease
- How to treat thromboembolic disease
- Some of the problems associated with thromboprophylaxis

Preventing thrombosis in pregnancy

- Individualized risk assessment
- Physical methods of prophylaxis
- Pharmacological methods of prophylaxis
- Who’s responsibility is it?

Risk assessment



Appendix I: Obstetric thromboprophylaxis risk assessment and management

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

Fewer than three risk factors

Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel → **LOWER RISK** — Mobilisation and avoidance of dehydration

APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis, oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥ 3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

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

- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

→ **HIGH RISK** — At least 6 weeks' postnatal prophylactic LMWH

- Caesarean section in labour
- BMI > 40 kg/m²
- Readmission or prolonged admission (> 3 days) in the puerperium
- Any surgical procedure in the puerperium except immediate repair of the perineum
- 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

→ **INTERMEDIATE RISK** — At least 10 days' postnatal prophylactic LMWH; NB if persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age > 35 years
- Obesity (BMI > 30 kg/m²)
- Parity > 3
- Smoker
- Elective caesarean section
- Family history of VTE
- Low-risk thrombophilia
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, PGP, long-distance travel
- Current pre-eclampsia
- Multiple pregnancy
- Preterm delivery in this pregnancy (< 37+1 weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (> 24 hours)
- PPH > 1 litre or blood transfusion

Two or more risk factors

Fewer than two risk factors → **LOWER RISK** — Early mobilisation and avoidance of dehydration

Antenatal and postnatal prophylactic dose of LMWH

Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily
Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily
Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily
Weight 131–170 kg = 80 mg enoxaparin/10000 units dalteparin/9000 units tinzaparin daily
Weight > 170 kg = 0.6 mg/kg/day enoxaparin / 75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin

RCOG Green-top Guideline No. 37a

33 of 40

© Royal College of Obstetricians and Gynaecologists

https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf

RCOG guidelines

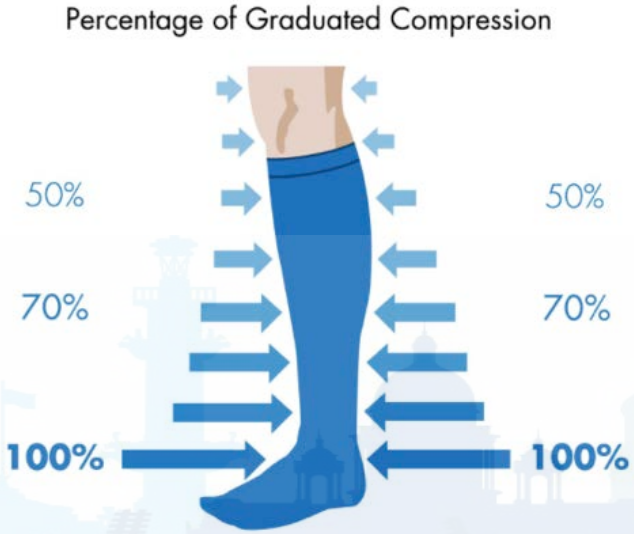
Antenatal thromboprophylaxis should begin as early in pregnancy as practical

LMWH are the agents of choice for antenatal thromboprophylaxis

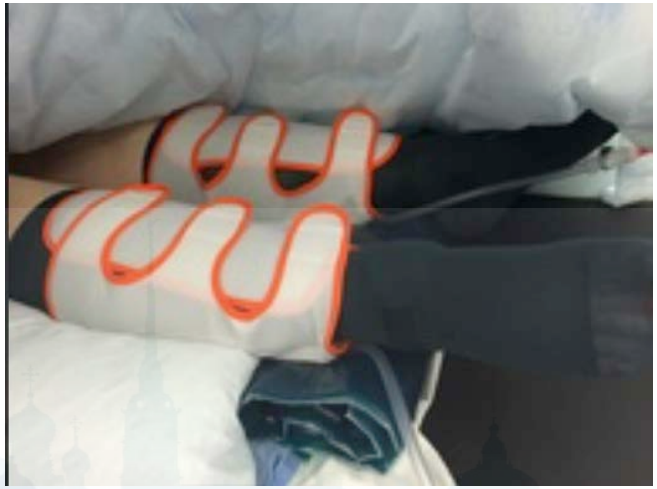
Any woman with three or more current or persisting risk factors should be considered for prophylactic LMWH antenatally

Physical methods of thromboprophylaxis

Graduated compression stockings



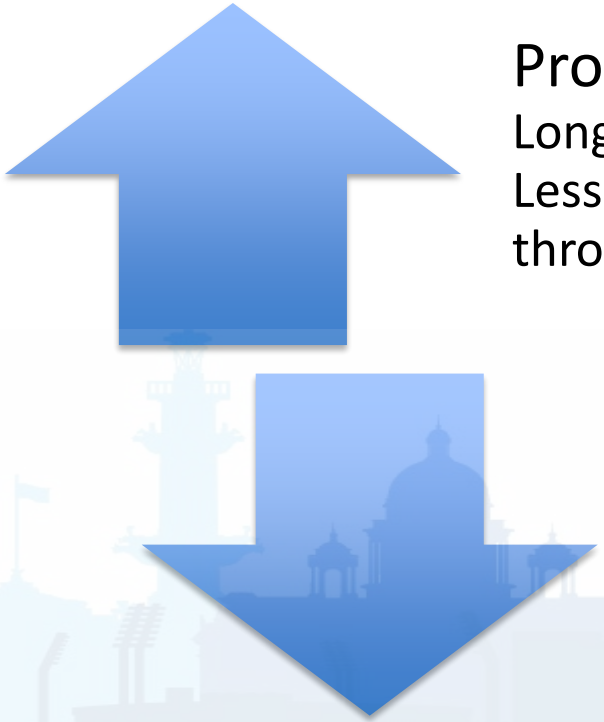
Mechanical sequential compression devices



Low molecular weight heparin

- Why are these the agents of choice?
  - Enhanced ratio of anti-Xa (antithrombotic) to anti-IIa (anticoagulant) activity reducing the risk of bleeding
  - Less binding to platelet factor 4 substantially reducing the risk of heparin-induced thrombocytopaenia
  - Less osteoporosis

Pros & cons of low molecular weight heparin



Pros

Longer acting, once daily dosing
Less osteoporosis, heparin induced thrombocytopenia

Cons

Products vary
Difficult to monitor
Still get some side effects

International recommendations

American College of Obstetricians and Gynecologists	Society of Obstetricians and Gynaecologists of Canada	Royal College of Obstetricians and Gynaecologists (RCOG)	Australia/New Zealand	American College of Chest Physicians
Heparin compounds are the preferred anticoagulant during pregnancy, specifically LMWH	LMWH is the preferred pharmacologic agent over UFH for treatment of VTE during pregnancy LMWH is the preferred pharmacologic agent over UFH for antepartum & postpartum thromboprophylaxis	LMWH is the preferred anticoagulant for treatment of acute VTE during pregnancy LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis Oral thrombin and Xa inhibitors should be avoided in pregnant women	Women with VTE in pregnancy should not be treated with vitamin K antagonists, such as warfarin. LMWH is preferred	For pregnant patients, recommend LMWH for prevention and treatment of VTE, instead of UFH For pregnant women, recommend avoiding the use of oral direct thrombin and factor Xa inhibitors

RCOG suggested doses for low molecular weight heparin thromboprophylaxis

Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/day)
< 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*	10 000 units daily	9000 units daily*
> 170 kg	0.6 mg/kg/day*	75 u/kg/day	75 u/kg/day*
High prophylactic dose for women weighing 50–90 kg	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly

*may be given in 2 divided doses

‘Newer antithrombotic drugs’ – fondaparinux

- Synthetic indirect inhibitor of factor Xa
- T ½ 17-21h, excreted in kidneys
- No heparin induced thrombocytopenia, osteoporosis

- Stop → insertion of regional anaesthetic:36-40h
- Insertion → dose: 6-8h

- <u>Pregnancy:</u>
  - Useful in women allergic to LMWH
  - Fetal safety?
  - Cross the placenta in small quantities
  - Several reports of the successful use of fondaparinux in pregnant woman have been published but important to recognize that many of these involve **second trimester or later exposure**

New drugs - enteral

	Dabigatran *pradaxa*	**Rivaroxaban** *Xarelto*	**Apixaben** *Eliquis*
Mechanism	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
T1/2	12-17h	5-9h	9-14h
Indications	Ortho DVT prophylaxis, AF	Ortho DVT prophylaxis, AF, DVT treatment & prophylaxis	Ortho DVT prophylaxis

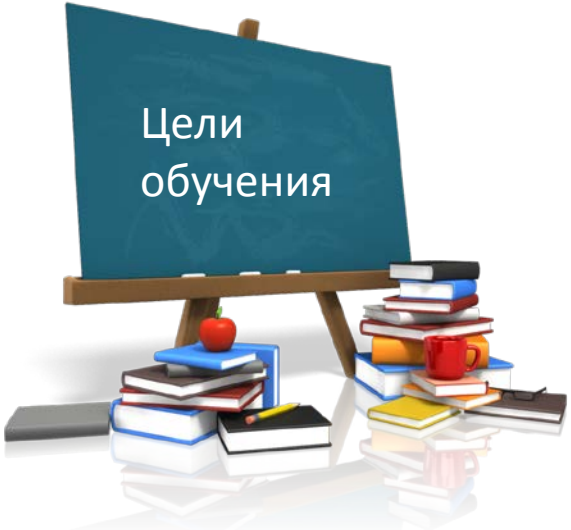
Are they coming to obstetrics?

- Safe in pregnancy/breastfeeding
  - NO data
- No ‘reversibility’, long T1/2
  - ?provision of epidurals/spinals
  - risk of haemorrhage

Are they coming to obstetrics?

- Safe in pregnancy/breastfeeding
  - NO data
- No ‘reversibility’, long T1/2
  - ?provision of CNB
  - Risk of haemorrhage

  - NOT ANY TIME SOON!



- Pathophysiology of thromboembolic disease in pregnancy
- How to prevent thromboembolic disease
- How to treat thromboembolic disease
- Some of the problems associated with thromboprophylaxis

Diagnosis & management of deep vein thrombosis in pregnancy

1. **START TREATMENT**

   Any woman with symptoms and/or signs suggestive of venous thromboembolism should have objective testing performed urgently and treatment with low-molecular weight heparin given until the diagnosis is excluded by objective testing

2. **INVESTIGATE**

   Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT

Diagnosis & management of deep vein thrombosis in pregnancy

1. **START TREATMENT**

   Any woman with symptoms and/or signs suggestive of venous thromboembolism should have objective testing performed urgently and treatment with low-molecular weight heparin given until the diagnosis is excluded by objective testing

2. **INVESTIGATE**

   Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT

- If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued
- If ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound should be repeated on days 3 and 7

Treatment doses of low molecular weight heparin

Table 1a. Initial dose of enoxaparin is determined as follows:

Booking or early pregnancy weight	Initial dose of enoxaparin
< 50 kg	40 mg twice daily or 60 mg once daily
50–69 kg	60 mg twice daily or 90 mg once daily
70–89 kg	80 mg twice daily or 120 mg once daily
90–109 kg	100 mg twice daily or 150 mg once daily
110–125 kg	120 mg twice daily or 180 mg once daily
> 125 kg	Discuss with haematologist

Table 1b. Initial dose of dalteparin is determined as follows:

Booking or early pregnancy weight	Initial dose of dalteparin
< 50 kg	5000 iu twice daily or 10 000 iu once daily
50–69 kg	6000 iu twice daily or 12 000 iu once daily
70–89 kg	8000 iu twice daily or 16 000 iu once daily
90–109 kg	10 000 iu twice daily or 20 000 iu once daily
110–125 kg	12 000 iu twice daily or 24 000 iu daily
> 125 kg	Discuss with haematologist

Table 1c. Initial dose of tinzaparin is determined as follows:

Initial dose of tinzaparin *(based on booking or early pregnancy weight)*
175 units/kg once daily

Are biomarkers useful in the detection of pulmonary embolus?

bjh research paper

The DiPEP (Diagnosis of PE in Pregnancy) biomarker study: An observational cohort study augmented with additional cases to determine the diagnostic utility of biomarkers for suspected venous thromboembolism during pregnancy and puerperium

Hunt et al, Br J Haematology, 2018

Blood samples from 310 pregnant/postpartum women with suspected pulmonary emboli and with diagnosed dee

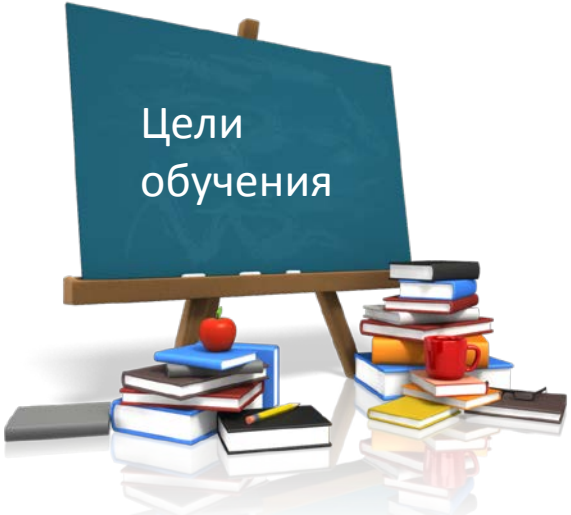
Thromboembo

Biomarkers as , C-reactive protein, Clauss

Take home message

No diagnostically useful threshold for diagnosing or ruling out thromboembolism was identified

In pregnancy and the puerperium, conventional and candidate biomarkers have no utility either for their negative or positive predictive value in the diagnosis of VTE

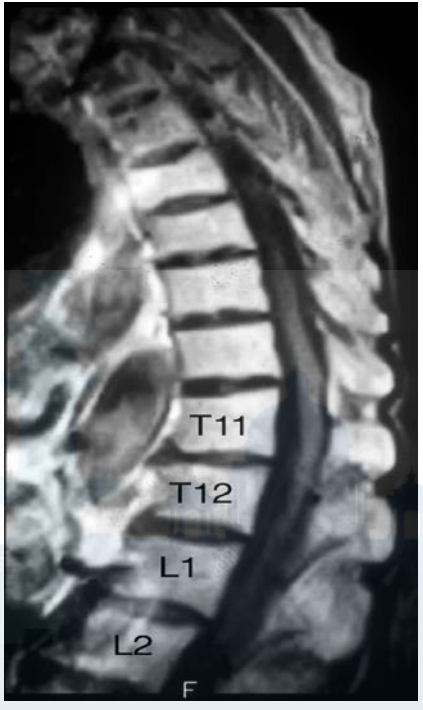


- Pathophysiology of thromboembolic disease in pregnancy
- How to prevent thromboembolic disease
- How to treat thromboembolic disease
- Some of the problems associated with thromboprophylaxis

Avoiding complications (epidural haematoma) associated with thromboprophylaxis

In 1997 the FDA issued a black box warning for LMWH and neuraxial blockade. There were more than 80 voluntary reports of epidural or spinal hematoma formation associated with the use of enoxaparin.

What was happening in the U.S.?



- Lack of guidelines
- Higher total daily dose (60 vs 40mg)
- Twice daily dosing
- More epidurals

(Europe? – likely under-reporting)

Practical management

- Clear guidelines for thromboprophylaxis
- Do you HAVE to do an RA?
  - Remifentanil
  - Other blocks (rectus sheath & TAP blocks)
  - Remove epidural catheters early

Practical management

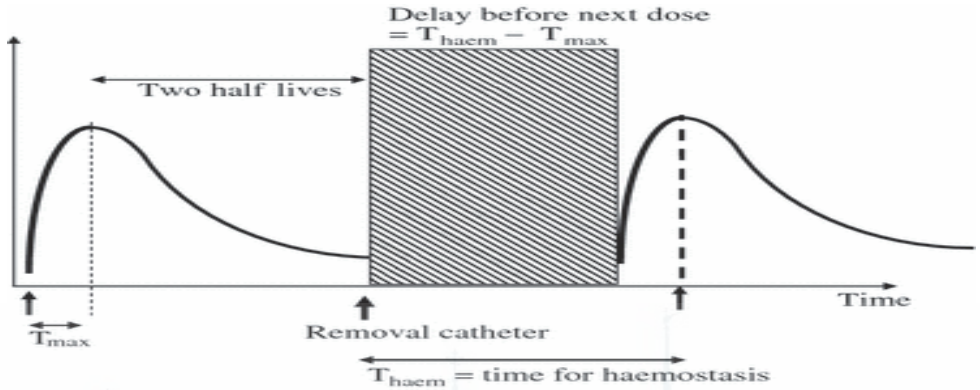
- Robust post-operative follow up and assessment……
- Watch out for persistent sensory/motor block
- Early MRI

LMWH

LMWH	USA	Germany	Spain	Austria	Belgium	UK
stop → insertion (prophylactic)	10-12h	10-12h	12h	12h	12h	12h
stop → insertion (therapeutic)	24h	24h	24h	24h	24h	24h
insertion → dose	6-8h	4h	6h	4h	4h	4h
stop → removal	10-12h	12h	12h		12h	12h
removal → dose	>2h		6h	4h	4h	4h

Adapted from British Journal of Haematology 2010

Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies.



- Suggests delaying removal of a neuraxial catheter until at least 2 T1/2 have elapsed for the specific anticoagulant involved. After 2 T1/2, only 25% of the medication remains active. *After this interval, elimination slows considerably so waiting longer only slightly decreases the residual drug concentration*

Rosencher et al, Anaesthesia 2007

Take home messages

1. Pregnant women are at increased risk of thromboembolic disease, the risk persists for 6 weeks after delivery
2. Low molecular weight heparin is the agent of choice for prevention and treatment
3. Insertion (or removal) of epidural or spinal anaesthesia must be carefully timed in women who receive LMWH

Съезд
Congress

АССОЦИАЦИЯ АКУШЕРСКИХ АНЕСТЕЗИОЛОГОВ-РЕАНИМАТОЛОГОВ

5-7 сентября 2018 / Санкт-Петербург
September 5-7, 2018 / St. Petersburg

Спасибо за ваше внимание