Thrombosis and Pregnancy

Dr. Catherine Bagot
Consultant Haematologist
Glasgow Royal Infirmary
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Venous Thromboembolism (VTE) in Pregnancy

- Prevalence
  - Morbidity and Mortality
- Risk factors
  - Pre-existing
  - Obstetric
- Prevention
- Treatment

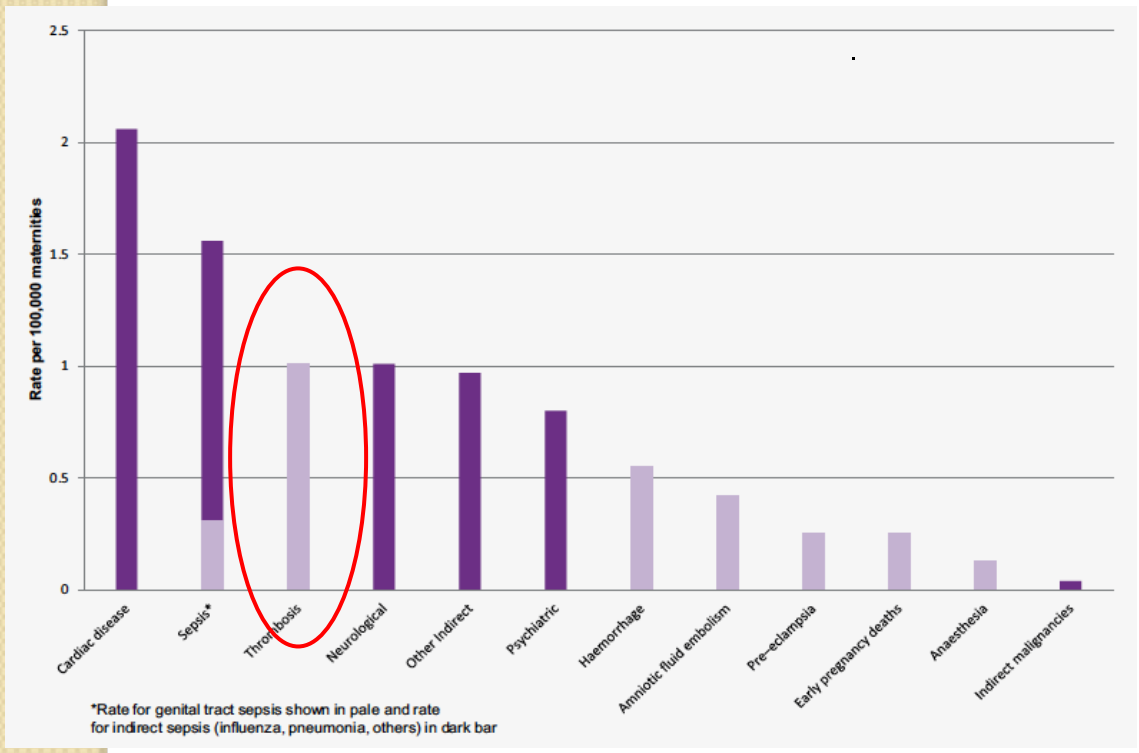
Prevalence of VTE in obstetrics

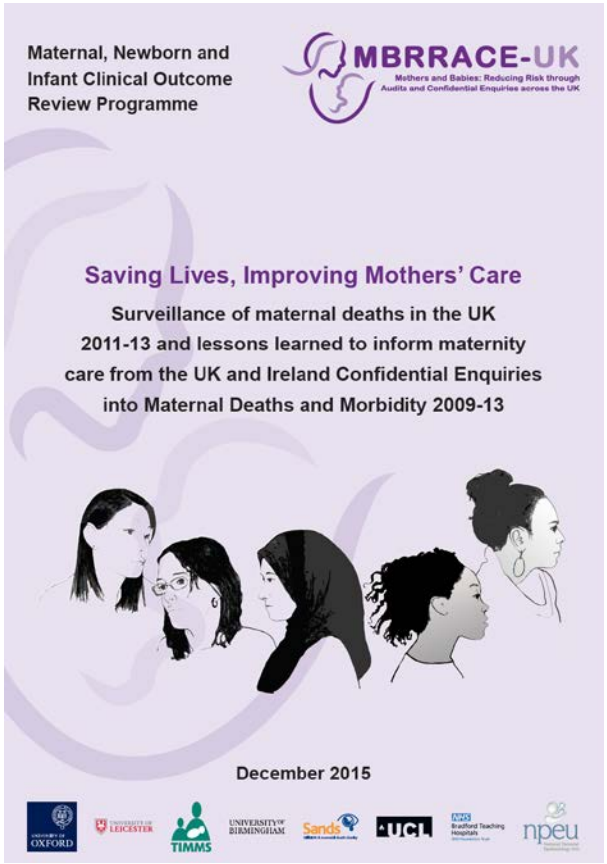
- Antenatal
  - 4-6x baseline risk compared to non-pregnant
  - Risk approximately equal throughout three trimesters
- Postnatal
  - 60x baseline risk compared to non-pregnant
  - Continues for approximately 3 months
  - Risk of PE particularly increased
- Overall risk 1-2:1000
  - 700,000 births/year
  - 700-1400 VTE/year
- Case fatality rate overall 1% (PE 3.5%)

Blano-Molina A, Thromb Haemost 2007;97:186-90
Heit JA, Ann Intern Med 2005;143:697-706
Pomp ER, J Thromb Haemost 2008;6: 632-7
Knight M, BJOG 2008;115:453–61

VTE and Pregnancy

- VTE is 3rd leading cause of maternal death
- Post thrombotic syndrome (PTS) common
- High risk of recurrence in subsequent pregnancies

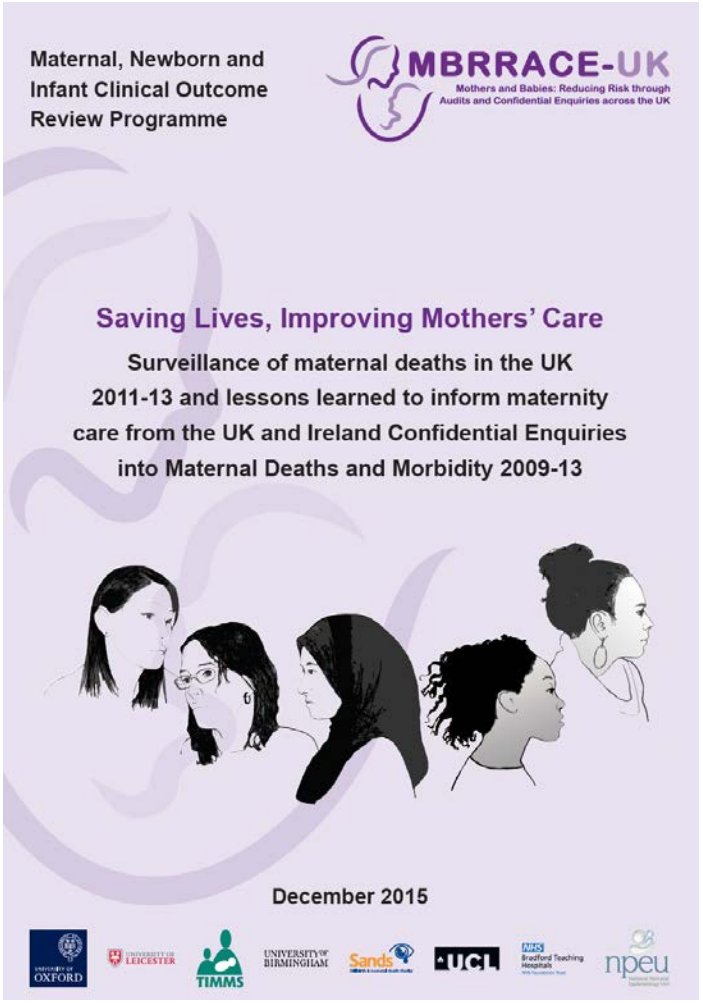




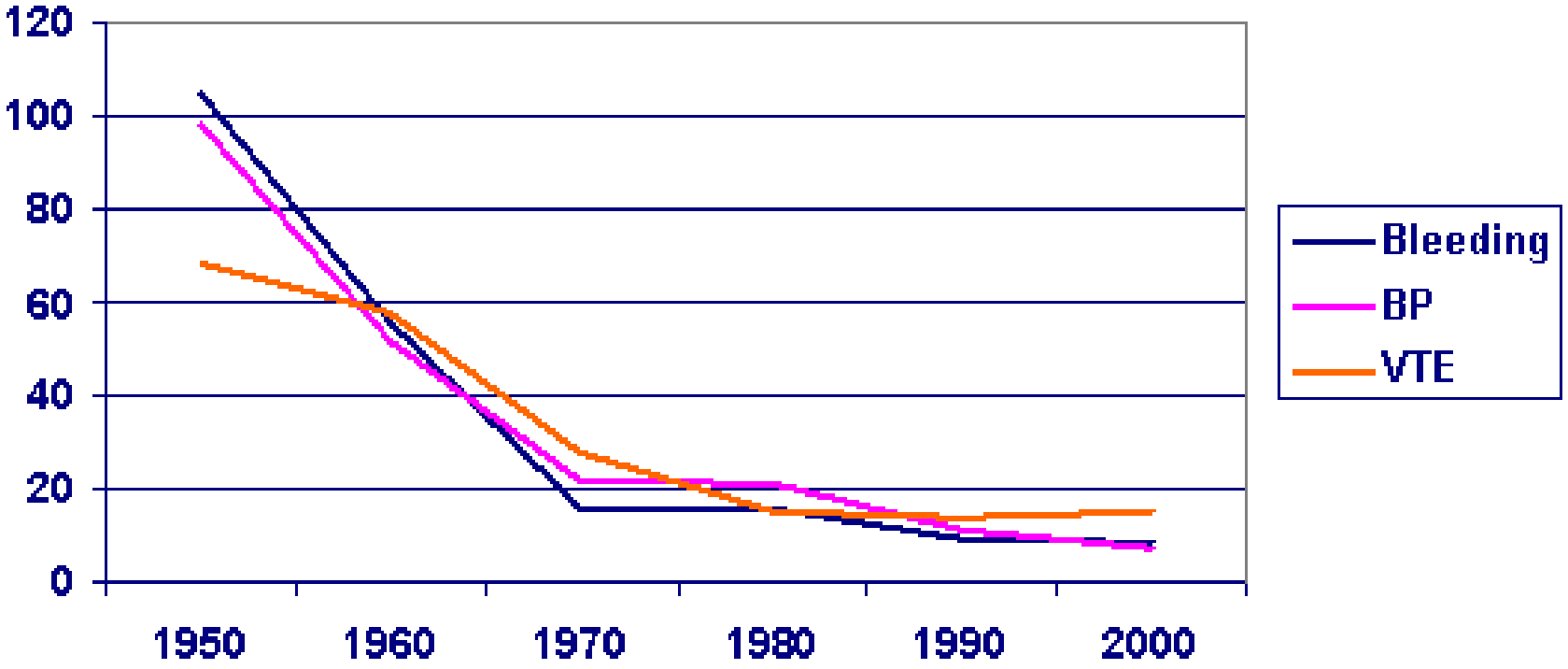
Mortality

- Confidential Enquiry into Maternal Deaths
  - Started 1952
  - Triennial report
  - Anonymous
  - Scotland since '85
  - Informs policy
    - Local
    - National
  - Most recent

    2011-13



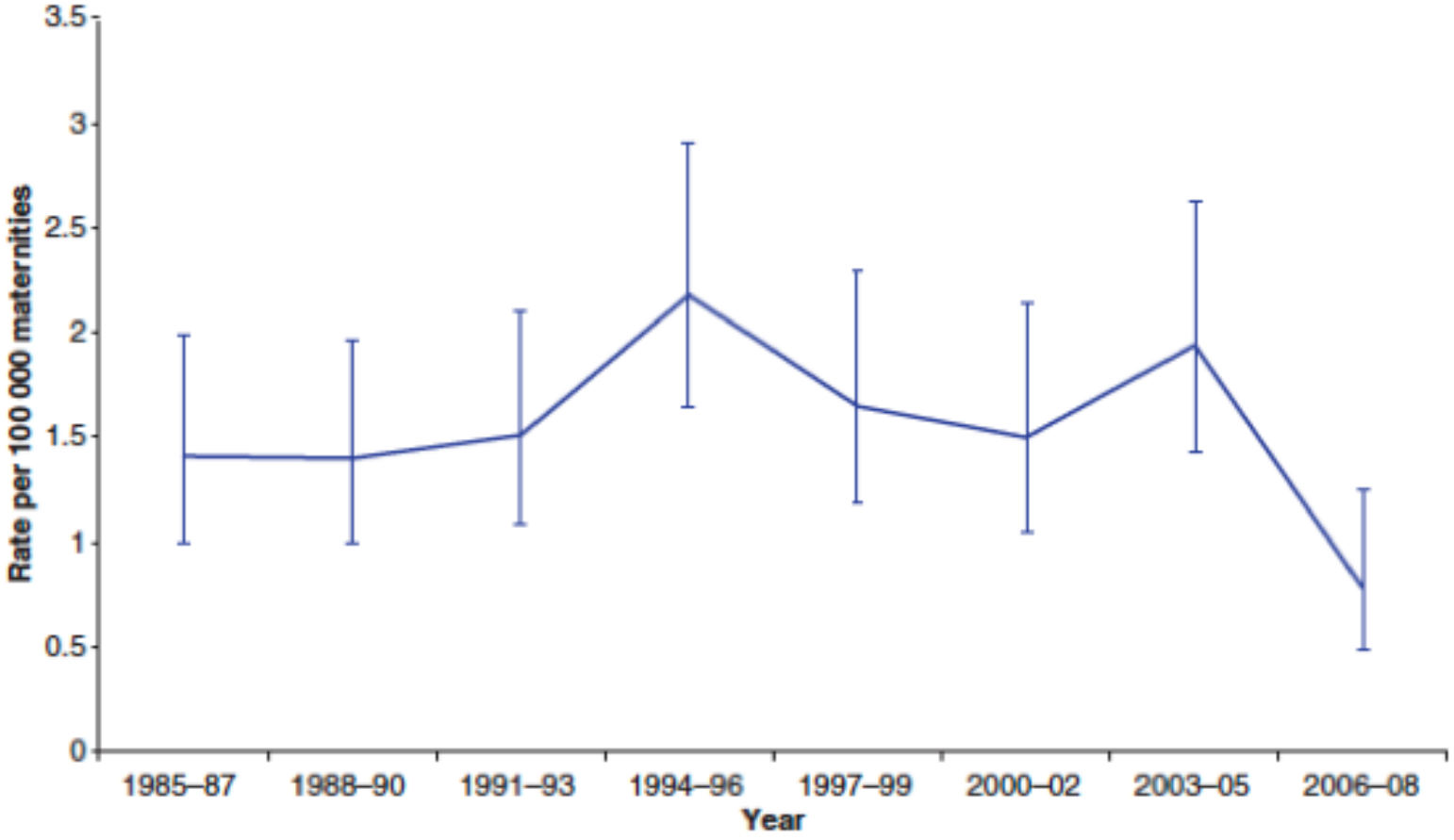
Deaths from VTE per million maternities 1950 - 2000.



Significant fall during 1960-70s – due to early mobilization
No more ‘lying in’.

http://www.drcog-mrcog.info/

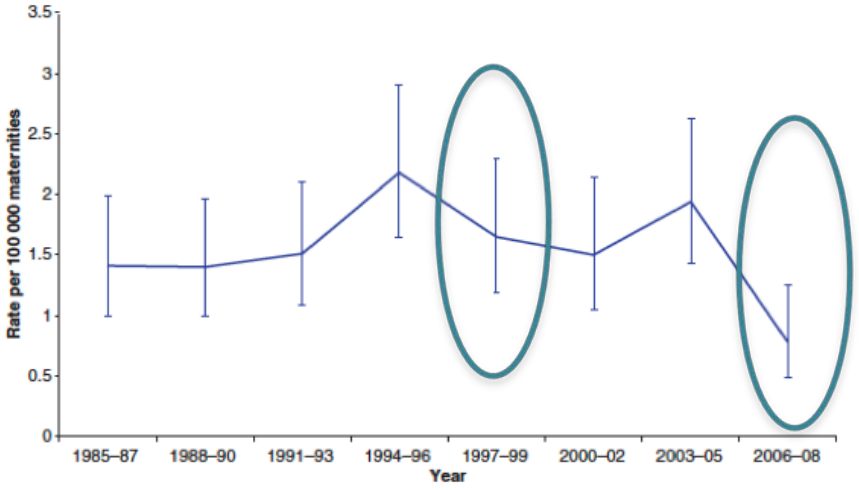
Maternal death rate from VTE (per 100,000)



Centre for Maternal and Child Enquiries (CMACE) BJOG 2011;118(Suppl. 1):1-203

Impact of RCOG guidelines

- RCOG guideline 1995
  - Highlighted risks of C-section and VTE
    - LMWH recommended with additional risk factors
- RCOG guideline 2004
  - Risk assessment following vaginal delivery
  - LMWH recommended with additional risk factors



Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Importance of body weight

In 2006-2008 report 12/18 women obese ?underdosing of LMWH

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

RCOG guideline, No 37a, 2009

Centre for Maternal and Child Enquiries (CMACE) BJOG 2011;118(Suppl. 1):1-203

Causes of maternal death (per 100,000)

Cause of death	2009-11			2010-12			2011-13		
	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
All Direct and Indirect deaths	253	10.63	9.36–12.03	243	10.12	8.89–11.47	214	9.02	7.85–10.31
Direct deaths									
*Sepsis**	15	0.63	0.35–1.04	12	0.50	0.26–0.87	7	0.29	0.12–0.61
Pre-eclampsia and eclampsia	10	0.42	0.2–0.77	9	0.38	0.18–0.71	6	0.25	0.09–0.55
Thrombosis and thromboembolism	30	1.26	0.85–1.80	26	1.08	0.71–1.59	24	1.01	0.65–1.5
Amniotic fluid embolism	7	0.29	0.12–0.61	8	0.33	0.14–0.66	10	0.42	0.20–0.78
Early pregnancy deaths	4	0.17	0.05–0.43	8	0.33	0.14–0.66	6	0.25	0.09–0.55
Haemorrhage	14	0.59	0.32–0.99	11	0.46	0.23–0.82	13	0.55	0.29–0.94
Anaesthesia	3	0.12	0.03–0.37	4	0.17	0.05–0.43	3	0.13	0.03–0.37
All Direct	83	3.49	2.78–4.32	78	3.25	2.57–4.05	69	2.91	2.26–3.68

Saving Lives, Improving Mothers' care UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13 MBRRACE 2015

Timing of VTE deaths

- 48 died (43 PE, 5 CVT)
- Antenatal 24 (50%)
  - 12 (50%) - First trimester
  - 6 (25%) - Second trimester
  - 6 (25%) - Third trimester
- Postnatal 24 (50%)
  - C-section 12 (50%)
    - 9 (66%)Emergency
    - 3 (33%) Elective
  - 10 (40%) vaginal
  - 2 (10%) post surgical procedures
- 16 - Late deaths (up to one year)
  - 13 PE; 3 CVT

Saving Lives, Improving Mothers' care UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13 MBRRACE 2015

Key Issues

- Just over 50% care suboptimal
- Just over 50% not compliant with RCOG guideline
- Risk assessment as early as possible in pregnancy
  - 52% women were not either not risk assessed or LMWH was under-dosed
  - 50% deaths in first trimester
    - Too early for current risk assessment
- Careful consideration of symptoms remains essential
  - Involve obstetricians when pregnant and post partum women present with symptoms of VTE to emergency care
- Avoid late and missed doses
  - Prescribe full course of LMWH for post partum period from secondary care

Risk factors for VTE in pregnancy

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	

Modified from RCOG guideline, No 37a, 2015

Risk factors for VTE in pregnancy

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)	

Modified from RCOG guideline, No 37a, 2015

Evidence for use of antepartum LMWH

- Some evidence
  - PMH
    - Idiopathic/estrogen induced
    - Associated thrombophilia
  - FH
    - Idiopathic/estrogen induced with associated thrombophilia
  - Synergism of risk factors
    - Very little
      - ART/multiple pregnancy (additive)
      - Immobility/BMI (multiplicative)

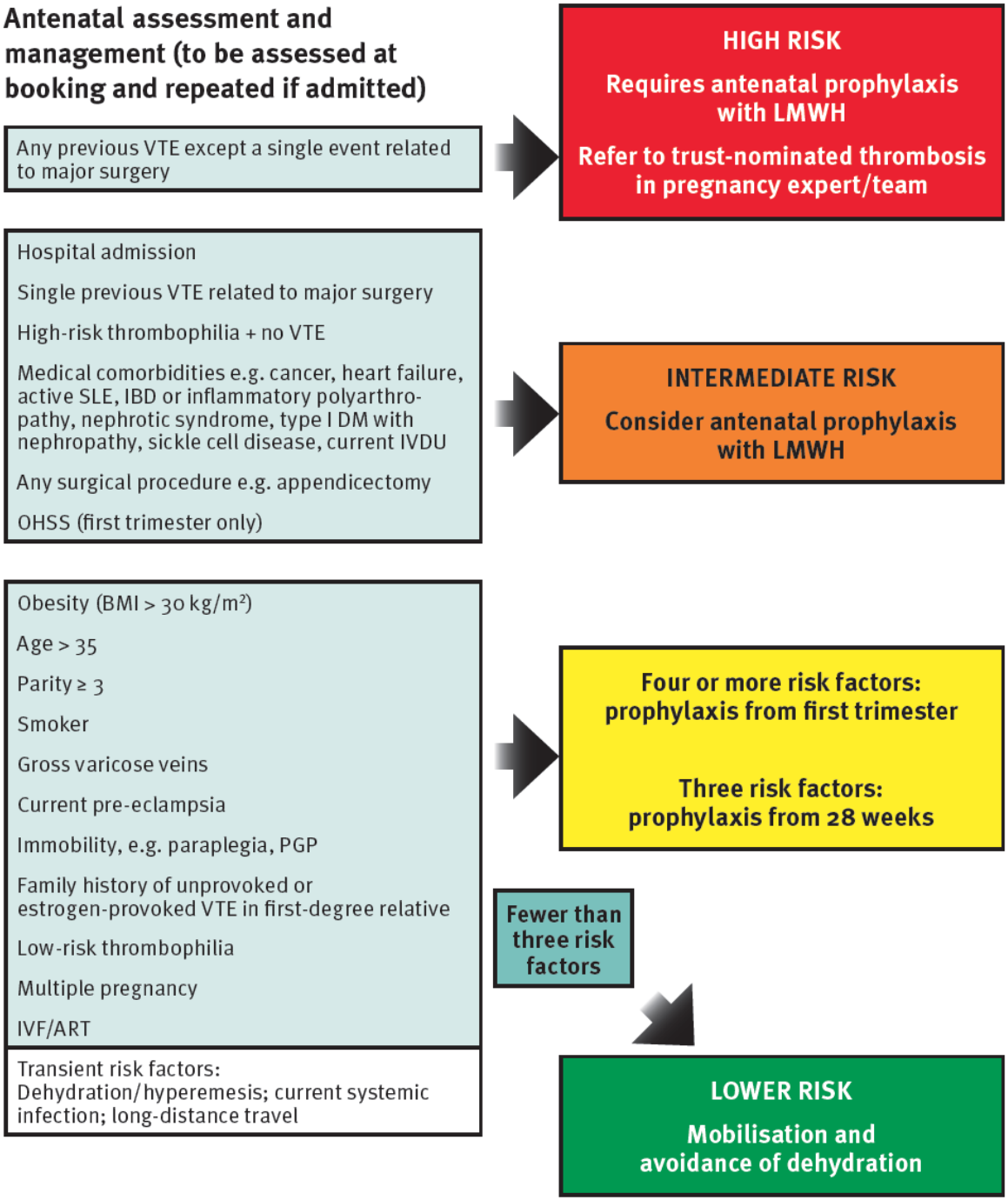
Jacobsen A, J Thromb Haemost 2008; 6: 905–12
Brill-Edwards P,. N Engl J Med . 2000 ; 343: 1439 - 1444

RCOG guideline 2015

Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or estrogen-provoked VTE in a first-degree relative when aged under 50 years should be considered for thrombophilia testing. This will be more informative if the relative has a known thrombophilia. [*New 2015*]

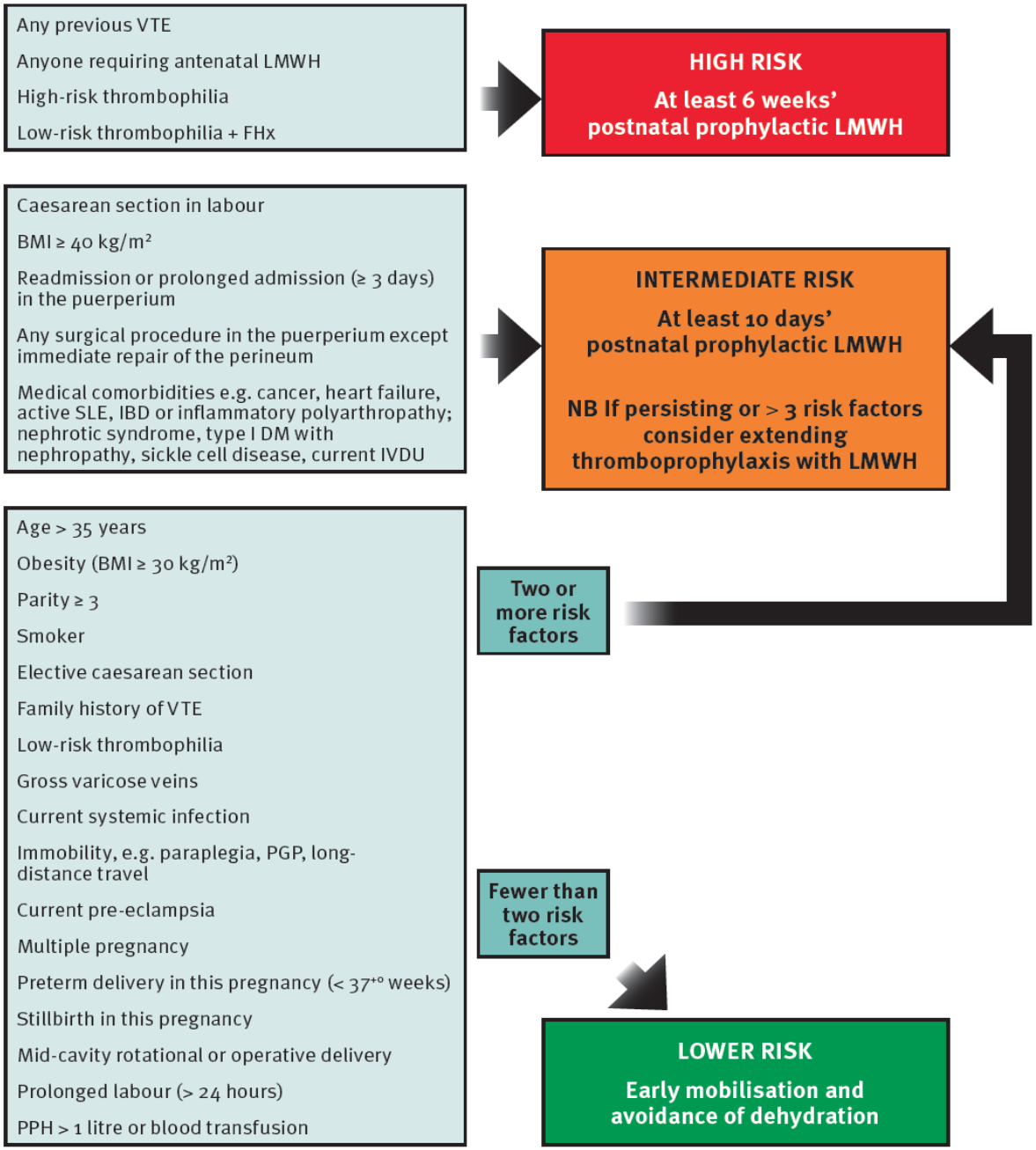
- Hypothesis
  - Thrombophilia has a strong phenotype
  - Thrombophilia affected relative
  - Therefore thrombophilia might affect you

RCOG guideline 37a, April 2015



Modified from RCOG guideline, No 37a, 2015

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



Modified from RCOG guideline, No 37a, 2015

Appendix III: Risk assessment for venous thromboembolism (VTE)

- 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.

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		

Modified from RCOG guideline, No 37a, 2015

VTE treatment

Significant changes in 2015 RCOG guidelines

Diagnosis – Significant changes

- If ultrasound negative and a high level of clinical suspicion
  - Anticoagulant treatment should be discontinued
  - Repeat USS on days 3 and 7
- Safe to discontinue anticoagulation
- Similar method used in non-pregnant population
- If do not discontinue anticoagulation between scans, extension will be prevented and false reassurance obtained

RCOG guideline 37b, April 2015
Chan et al., CMAJ 2013;185:E194–200

Diagnosing PE

- Perform CXR and ECG
- Suspected PE with symptoms and signs of DVT
  - Compression duplex ultrasound should be performed
- Suspected PE without symptoms and signs of DVT
  - Ventilation/perfusion (V/Q) lung scan
  - Computerised tomography pulmonary angiogram (CTPA) (preferred if CXR abnormal)
- Advice to women with suspected PE
  - Compared with CTPA
    - V/Q scanning slightly increased risk of childhood cancer
    - Lower risk of maternal breast cancer
    - In both situations, the absolute risk is very small

RCOG guideline 37b, April 2015

Treatment – Significant changes

- LMWH can be given once daily or in two divided doses
  - Multicentre study - 60% units give once daily
  - UKOSS study - 49% units give once daily
  - Aus/NZ guidelines state no evidence to prefer either
  - Data for once daily dosing with tinzaparin
  - Half life of LMWH increases during pregnancy with once daily dosing regimen
- Advantages
  - Patient satisfaction
  - Improved chance of safe regional anaesthesia use

RCOG guideline 37b, April 2015; Voke et al., Br J Haematol 2007;139:545–58; Patel et al., Circulation 2013;128:1462–9; Knight et al., BJOG 2008;115:453–61; McLintock et al., Aust N Z J Obstet Gynaecol 2012;52:14–22; Nelson-Piercy et al., Eur J Obstet Gynecol Reprod Biol 2011;159:293–9

Dosing of LMWH in pregnancy

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

- Issues
  - Syringe sizes not available in 90 mg
  - Check antiXa if syringe size is >10% from1.5mg/kg dose
    - e.g. 55kg = 1.5x55 = 82.5 mg
    - 100mg, 17.5% larger than recommended dose

RCOG guideline 37b, April 2015

Treatment

- Postpartum warfarin should be avoided until at least the fifth day (for longer in women at increased risk of postpartum haemorrhage)
  - No evidence for advice
  - Higher doses may be required with associated close monitoring
- Direct oral anticoagulants
  - Suitable alternative if not breastfeeding
  - More convenient for mother
    - No monitoring
    - Not affected by diet/most drugs
  - Probably should also wait 5 days
    - Possible signal of increased menstrual loss

Treatment – new information

- Following a DVT, graduated elastic compression stockings should be worn on the affected leg to reduce pain and swelling
  - Role of compression stockings in the prevention of post-thrombotic syndrome remains unclear.
- SOX study
  - Placebo vs. compression stocking
  - No difference in outcomes at 2 years

Kahn et al., Lancet 2014, 383: 880

Any Questions??

catherine.bagot@ggc.scot.nhs.uk