What's new in VTE in Pregnancy: Prevention and Management

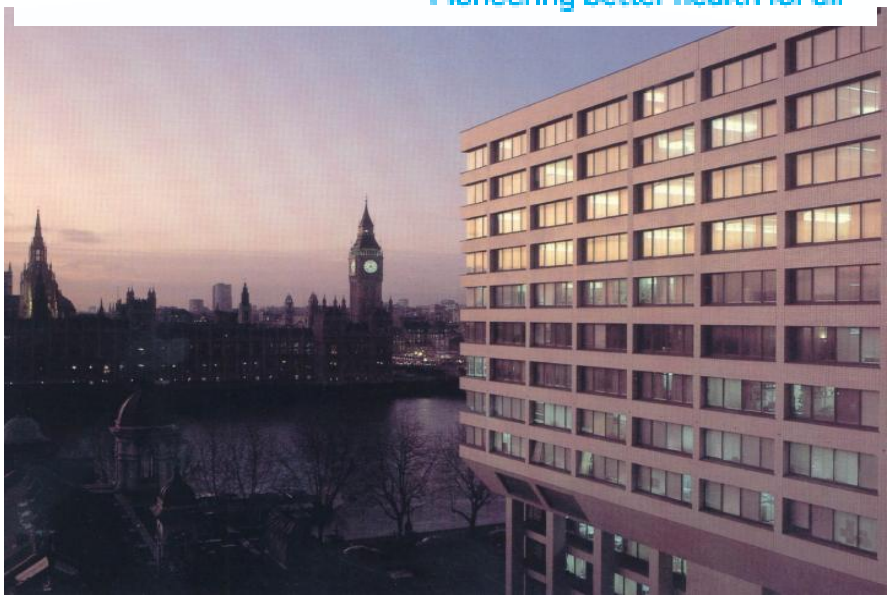
Catherine Nelson-Piercy

Guy's & St Thomas' Foundation Trust and

Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare Trust

KING'S HEALTH PARTNERS

Pioneering better health for all



Guy's and St Thomas' NHS
NHS Foundation Trust

Imperial College Healthcare NHS
NHS Trust

Disclosures

- I am lead developer of RCOG Green Top Guideline on thromboprophylaxis in pregnancy
- I have received lecturing fees from Sanofi-Aventis, Leo-Pharma

Lecture Plan

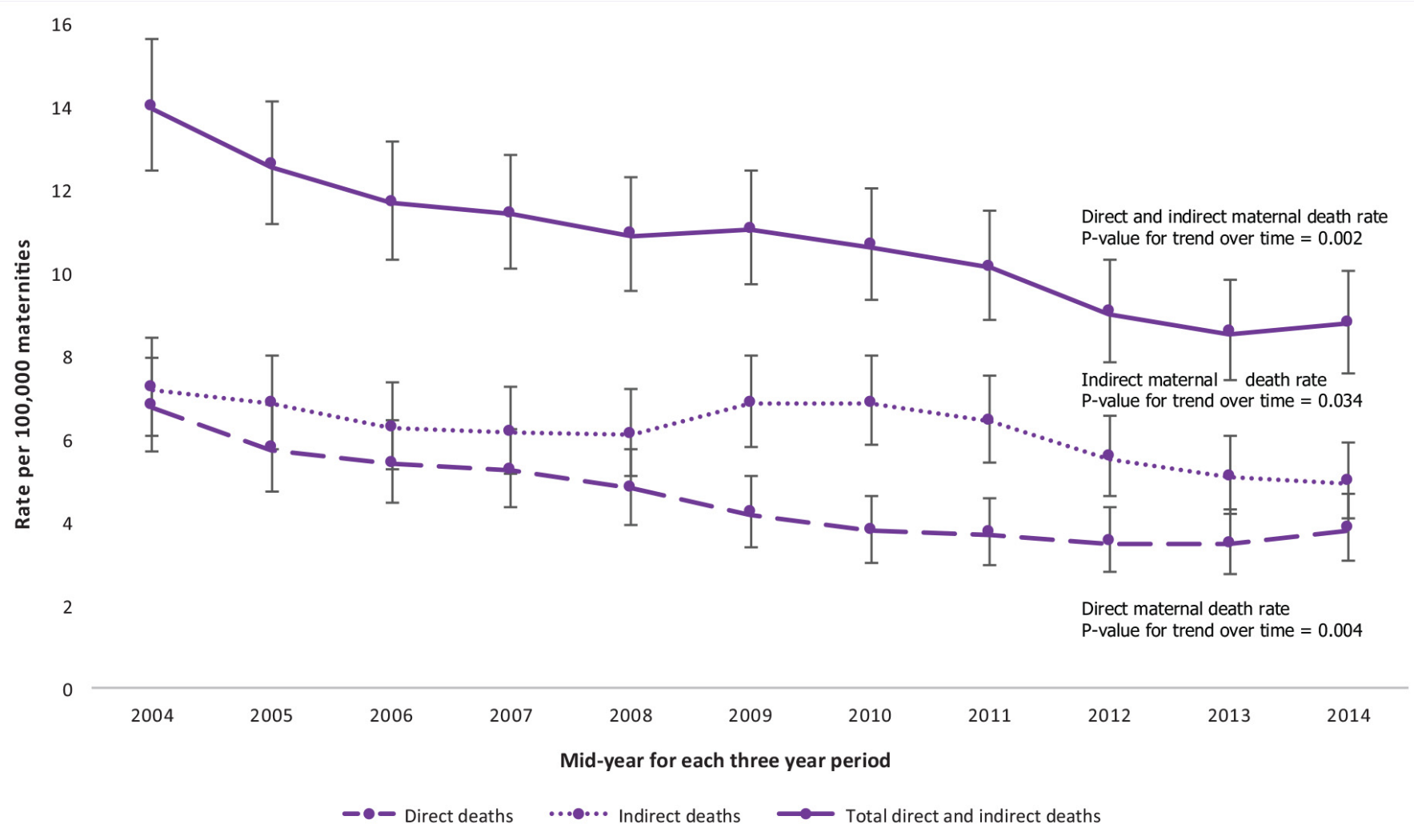
IMPORTANCE

PREVENTION- the RCOG guideline

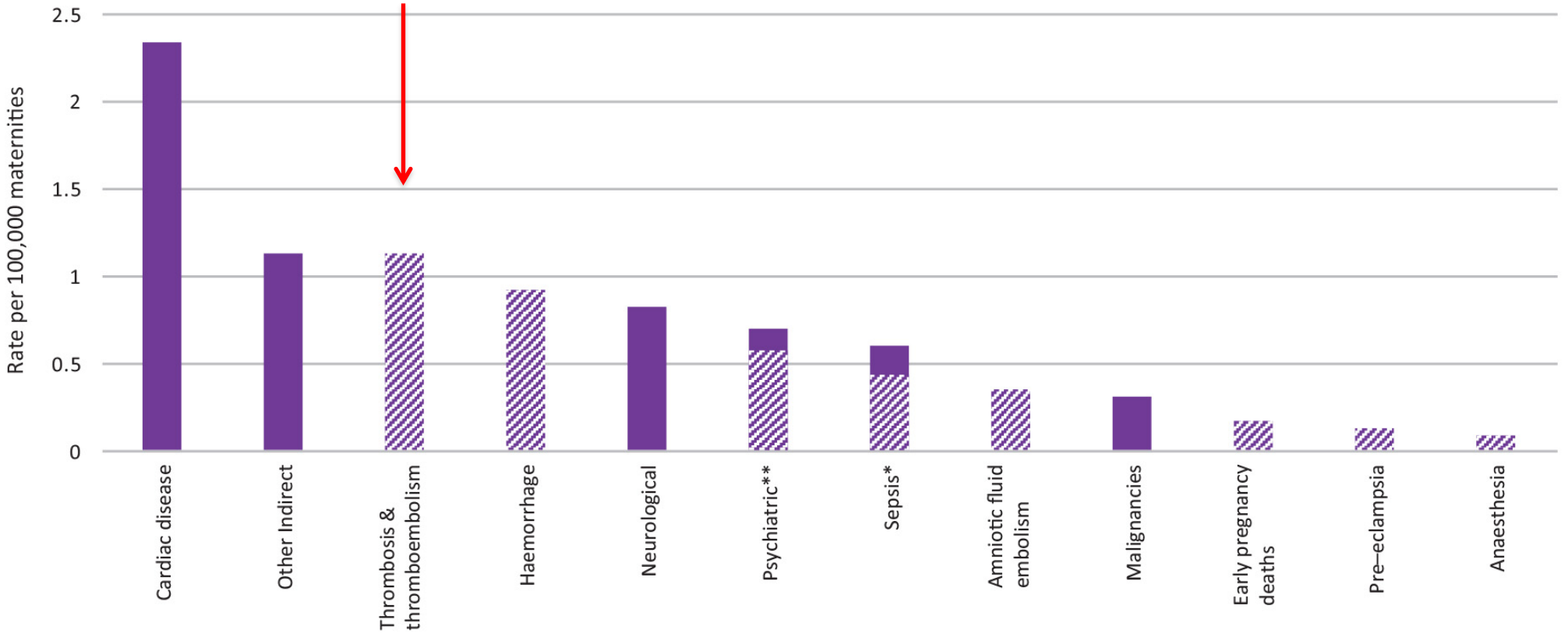
CONTROVERSIES IN DIAGNOSIS

TREATMENT OF ACUTE VTE

Maternal mortality UK 2003-15



Causes of maternal death 2013-15



The RCOG guidelines

Royal College of Obstetricians & Gynaecologists

Treatment

Prevention

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b

April 2015

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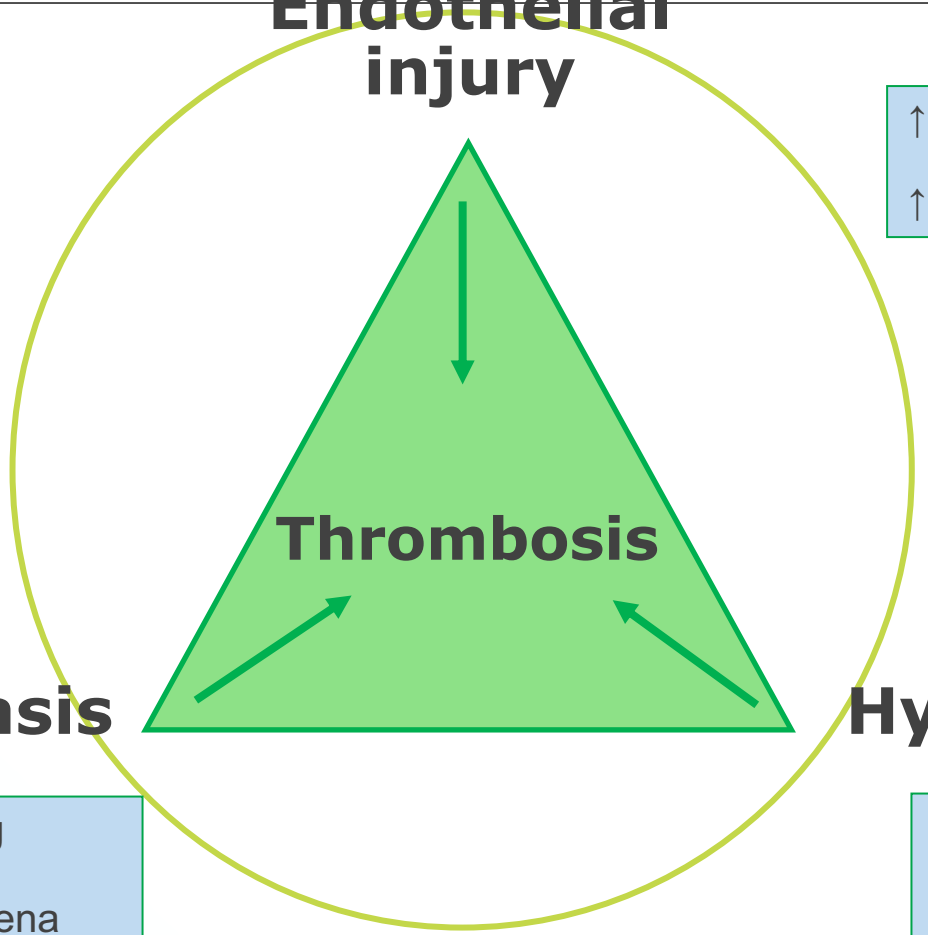
Pathogenesis: Virchow's triad



↑ Venous distension causing endothelial injury
↑ Trauma during delivery

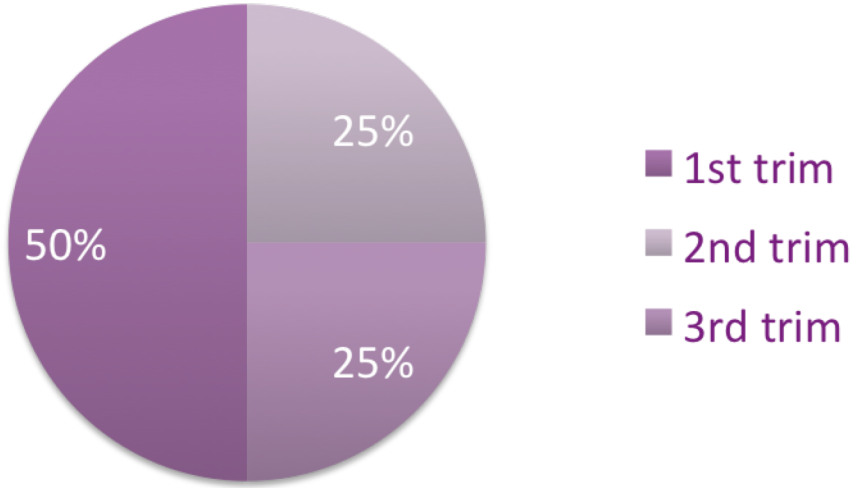
↑ Sluggish blood flow during pregnancy
↑ Compression on inferior vena cava by enlarging uterus
↑ Rest/supine position later in pregnancy

↑ Coagulation factors
↓ Natural inhibitors of coagulation
↓ Fibrinolytic activity

James. *Hematology Am Soc Hematol Educ Program* 2009;277–85
Kyrle and Eichinger *Blood* 2009;11:1138–9

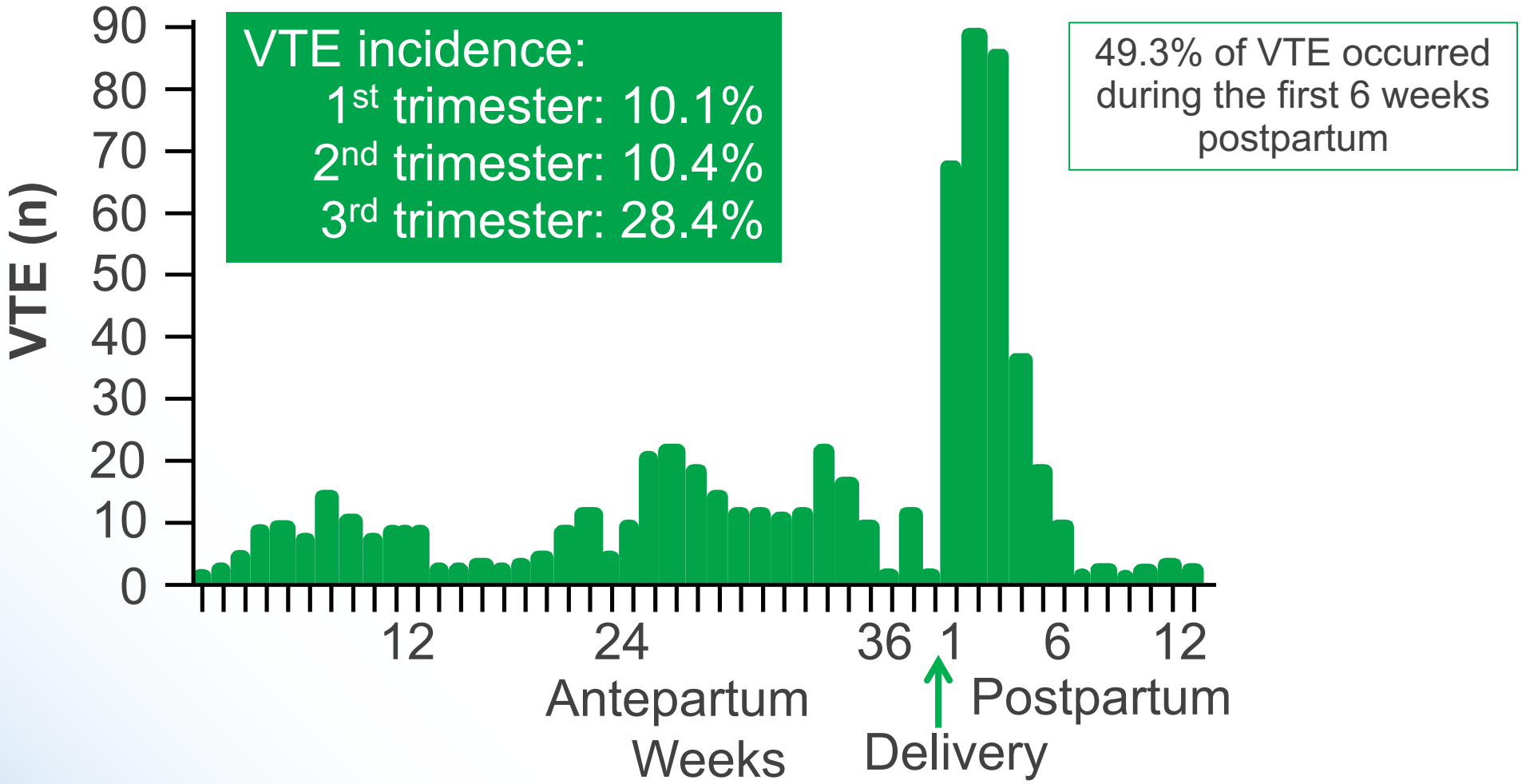
Timing of deaths from VTE

- 50% (24) thromboses occurred antenatally (some died postnatally)



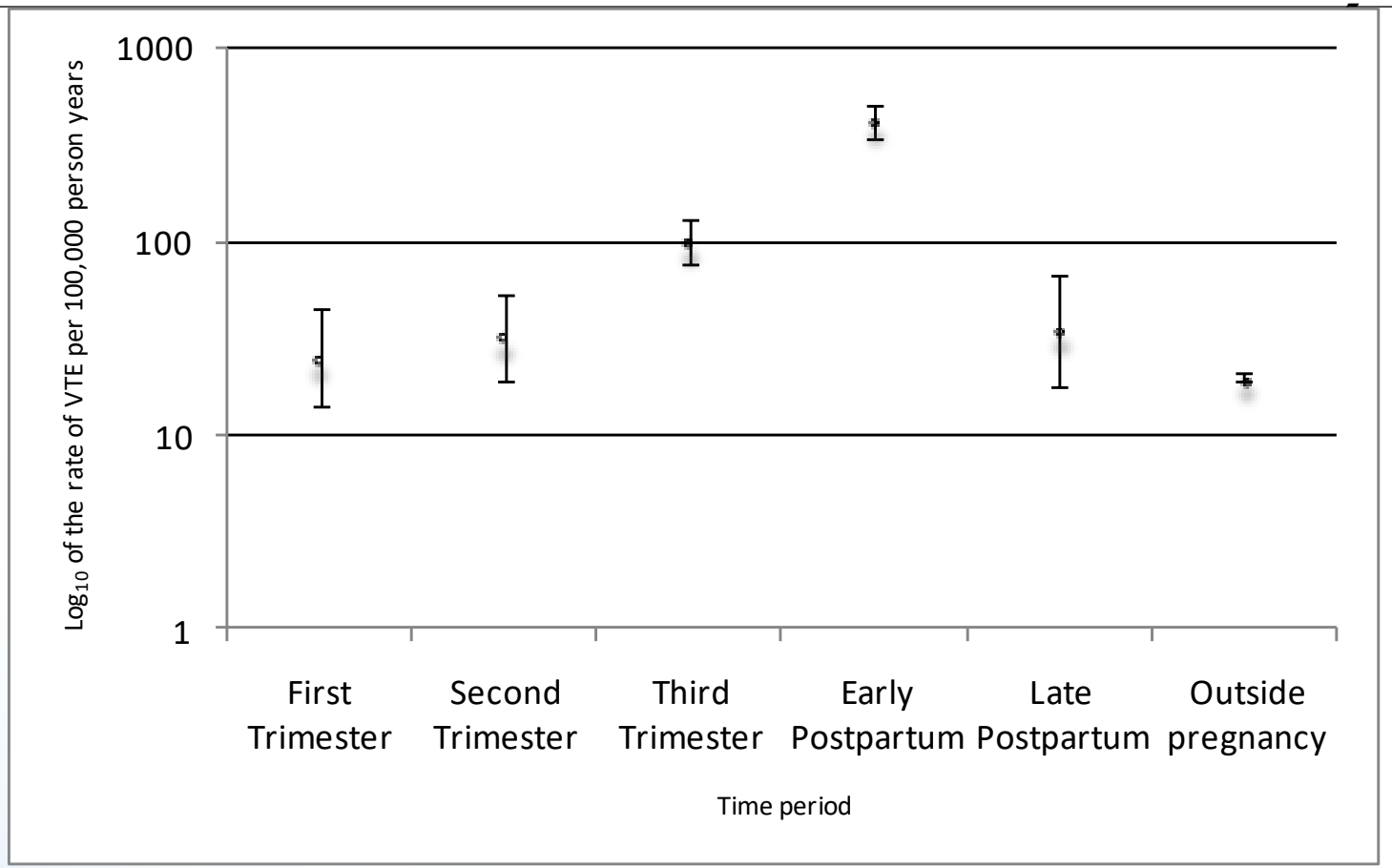
- 50% (24) occurred postnatally
  - 50% (12) delivered by CS (9 emCS; 3 elCS)
  - 10 delivered vaginally
  - 2 post surgical procedures in early pregnancy

Distribution of VTE in pregnancy and puerperium



Jacobsen *et al*. *Am J Obstet Gynecol* 2008;198(2):233.e1–7

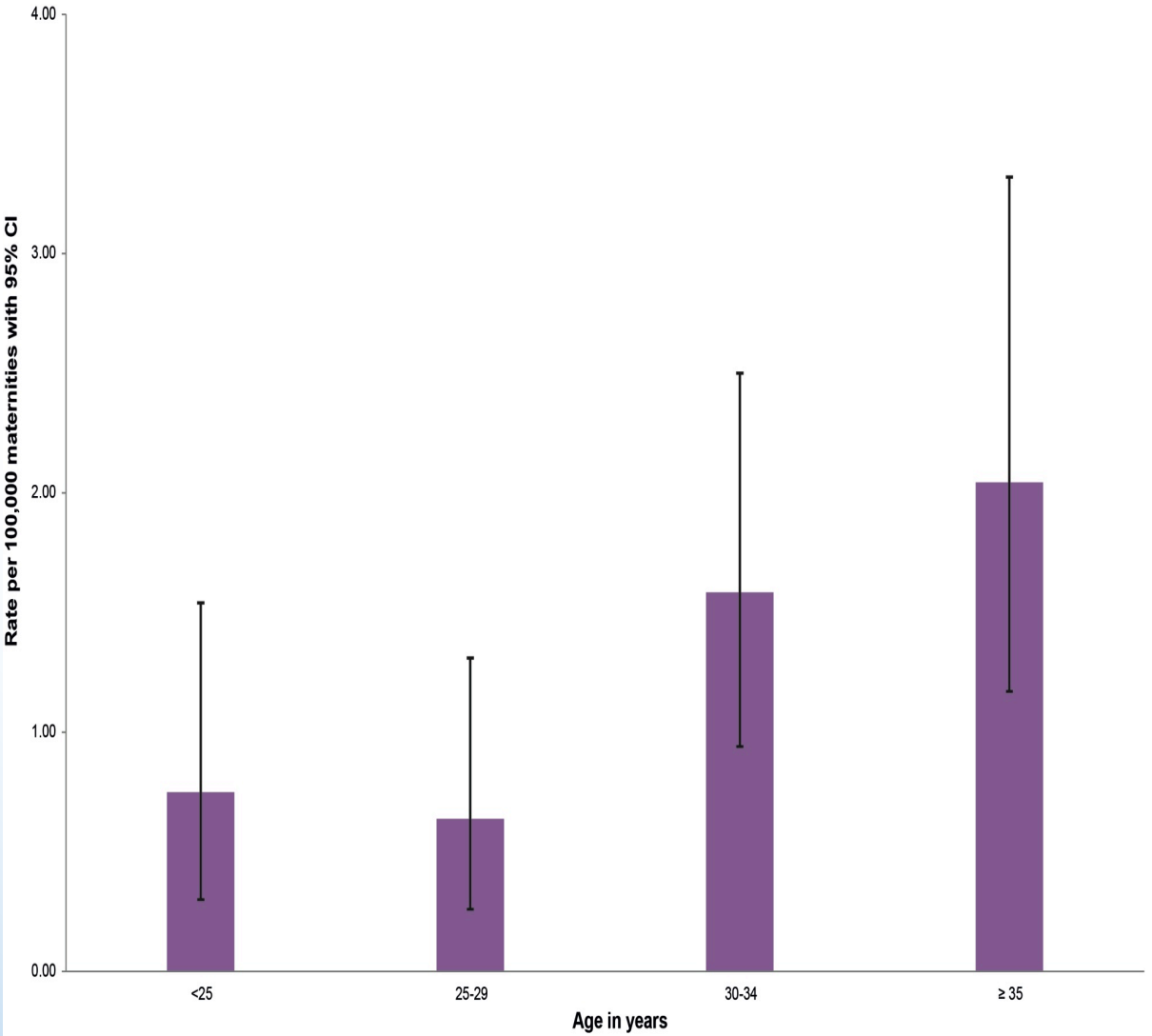
Figure 2: Log_{10} of the rate of VTE and 95% confidence intervals during different time periods during and outside pregnancy



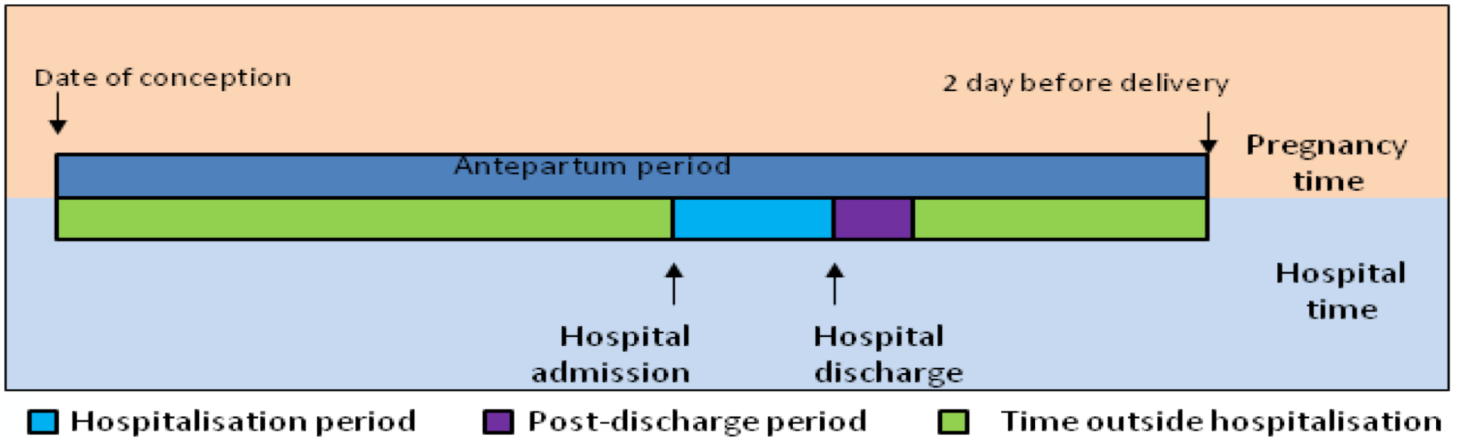
Outside pregnancy: Includes time for ever pregnant women spent outside antepartum and postpartum period and all time for women with no recorded pregnancy during study period
Early postpartum: First six weeks from date of delivery
Late postpartum: Subsequent six weeks postpartum

Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: A population-based cohort study. *Br J Haematol.* 2012 Feb;156(3):366-73.

Age


4.00
3.00
2.00
1.00
0.00
Rate per 100,000 maternities with 95% CI
<25
25-29
30-34
≥ 35
Age in years

Rate of VTE per 100,000 person years by antenatal admission to hospital and after hospital stay

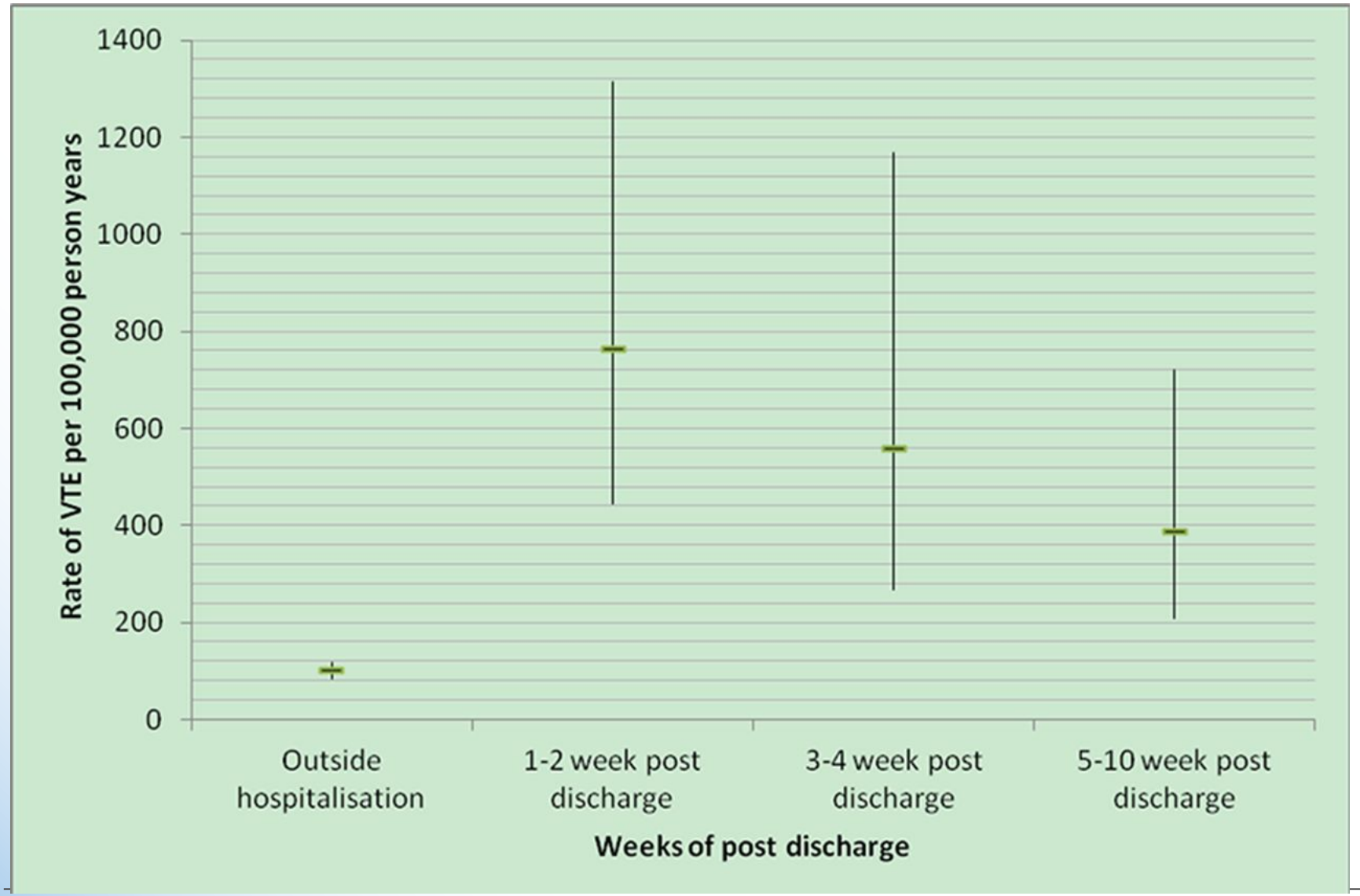


Variable	No of VTE	Rate* (95% CI)	Adjusted IRR (95% CI)†
Time outside hospital	150	97 (83 to 114)	1.00
Hospital admission	6	1752 (787 to 3900)	17.5 (7.69 to 40.0)
After discharge	20	676 (436 to 1048)	6.27 (3.74 to 10.5)
Variation by duration of hospital stay (combining admission/after discharge)			
Time outside hospital	150	97 (83 to 114)	1.00
<3 days	13	558 (331 to 943)	4.05 (2.23 to 7.38)
≥3 days	13	1511 (858 to 2661)	12.2 (6.65 to 22.7)

IRR=incidence rate ratio.
*Rate calculated per 100 000 person years.
†Adjusted for maternal age, calendar year, BMI, gestational infection, cardiac disease, varicose vein, gestational diabetes, and hyperemesis.

Sultan A et al. BMJ 2013;347:bmj.f6099

Fig 2 Rate of venous thromboembolism per 100 000 person years by weeks after discharge during antepartum period: 12 events in weeks 1-2 after discharge, 7 events in weeks 3-4 after discharge, and 12 events in weeks 5-10 after discharge.



Sultan A et al. BMJ 2013;347:bmj.f6099

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.

California, 2005-2010

1.7 million women, first delivery

1015 thrombotic events in 1 year and 24 weeks post delivery

47 MI; 248 CVA; 720 VTE

This article was published on February 13, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1311485

Weeks Post partum	VTE OR	95% CI
0-6	**12.1**	7.9 to 18.6
7-12	**2.2**	1.4 to 3.3
13-18	**1.6**	1.0 to 2.5
18-24	0.9	0.5 to 1.4

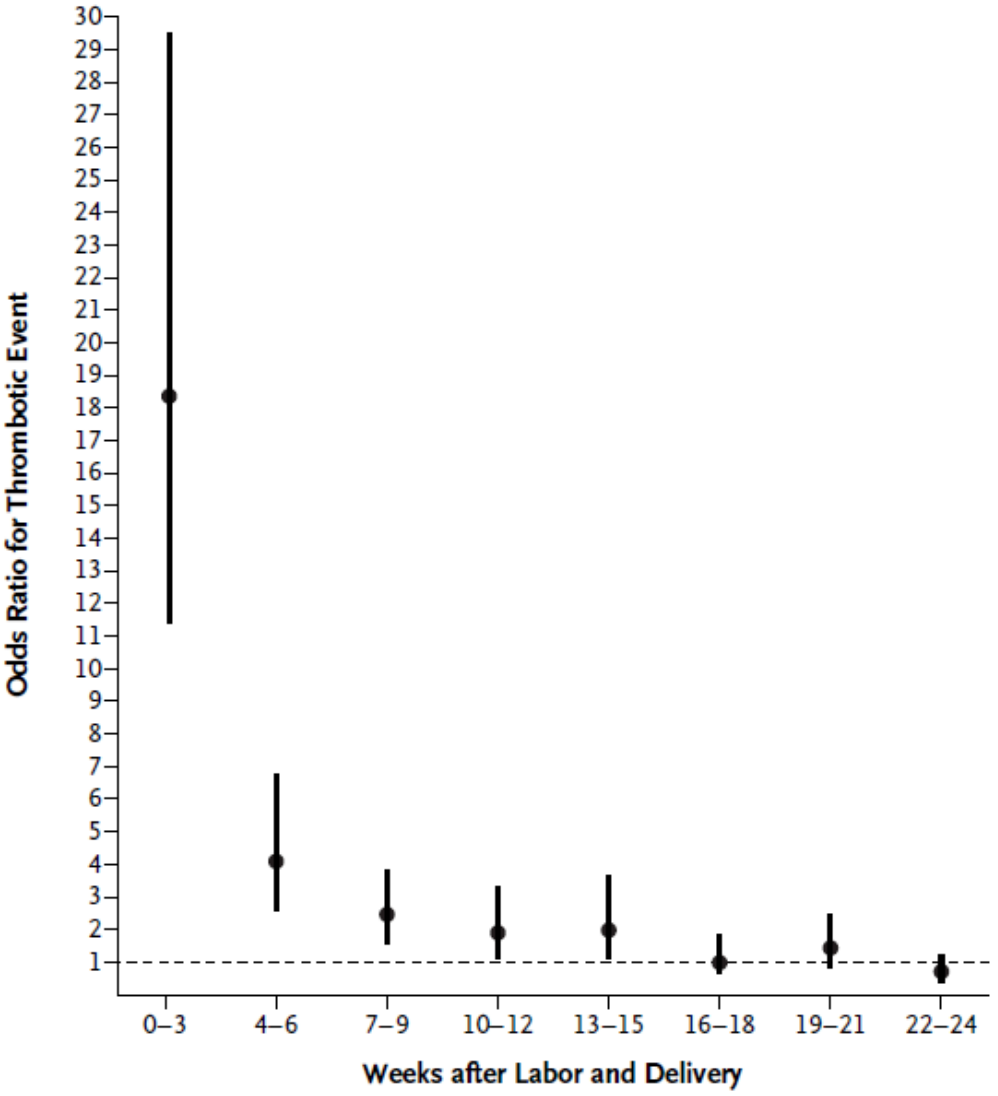


Figure 1. Risk of a Thrombotic Event, According to the Interval after Delivery.

Shown are the results of a post hoc exploratory analysis of the risk of a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism across sequential 3-week periods after labor and delivery, as compared with each patient's risk during the same period 1 year later. The thrombotic risk was still increased during the period of 13 to 15 weeks after delivery (odds ratio, 2.0; 95% CI, 1.1 to 3.6) but was no longer elevated in the period of 16 to 18 weeks after delivery (odds ratio, 1.0; 95% CI, 0.6 to 1.8). The vertical lines indicate 95% confidence intervals.

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 oestrogen-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, β_2-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 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

Absolute and relative rates of VTE by risk factors Postpartum

Variable	VTE	Rate[1]	95 %CI	IRR[2]	95%CI
Age=35 – 44 years	81	497	399 – 618	**1.51**	1.15 – 1.98
Obese (≥30)	79	926	742 – 1554	**3.75**	2.76 – 5.07
Current smokers	80	403	324 – 502	**1.31**	1.01 – 1.71
Caesarean delivery	83	637	513 - 790	**1.99**	1.52 – 2.58
3 or more previous births	25	904	611 – 1338	**2.07**	1.34 – 3.20
Stillbirth	6	2444	1098 – 5440	**6.24**	2.77 – 14.1
Pre-term birth	51	854	649 – 1124	**2.69**	1.99 – 3.65
Obstetric haemorrhage	10	963	518 – 1791	**2.89**	1.53 – 5.43
Acute systemic infection	43	455	337 - 614	1.33	0.96 – 1.85
Varicose veins	25	1330	899 – 1969	**3.83**	2.51 – 5.82
Cancer	5	446	185 – 1073	1.21	0.49 – 2.96
Inflammatory bowel disease	5	1514	630 – 3638	**4.56**	1.88 – 11.0
Cardiac disease	2	2258	646 - 10335	**6.58**	1.63 – 26.5

Sultan AA et al. Blood. 2013 May 9;121(19):3953-61

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*
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		

Abbreviations: ART assisted reproductive technology; IVF in vitro fertilisation; OHSS ovarian hyperstimulation syndrome; VTE venous thromboembolism.

* If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.

[b] BMI ≥ 30 = 1; BMI ≥ 40 = 2

Case 1

39 yr old multip, 38 weeks

Secondary infertility; IVF pregnancy

Admission for ovarian hyperstimulation syndrome

A+E: C/O swollen, painful left leg for 3 weeks

Sudden onset left sided pleuritic pain last night

SOB since

O/E dyspnoeic, RR 34, SOBOE undressing

Pulse 118, BP 104/66

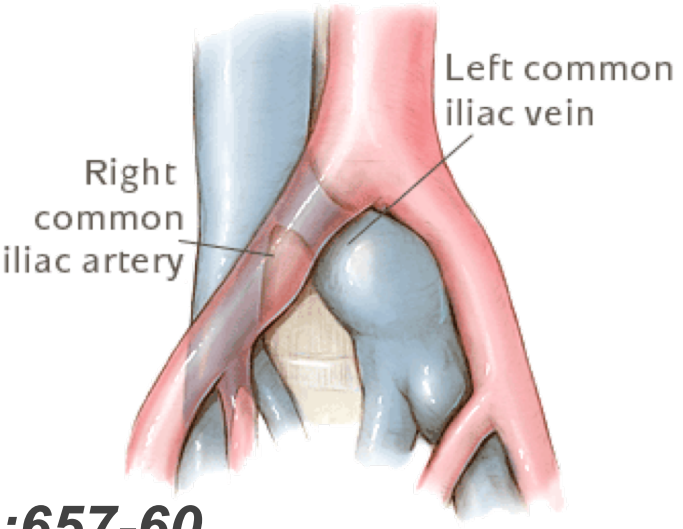
Oxygen saturation 92%

Diagnosis of DVT in Pregnancy

88% on left (vs. 55% in non pregnant)

71% proximal (vs. 9% in non pregnant)

- 64% were restricted to the iliac and/or femoral vein.



Chan WS et al. CMAJ 2010; 182:657-60

Diagnosis

DVT

- Doppler US

PE

- CXR
- V/Q Lung scan
- CTPA

D dimers are useless!!

Clinical prediction rules are also useless!!

Diagnosis - problems

US may miss below knee / above inguinal ligament. Solution:

If US negative and high level of clinical suspicion of DVT……

- **stop anticoagulation and repeat US day 3 and 7**
- **Do MR venogram**

Prevalence of ultimately diagnosed PE in pregnant women with suspected PE is 2–6%. Solution:

- **Stop irradiating women without good history!**
- **Half dose perfusion only**

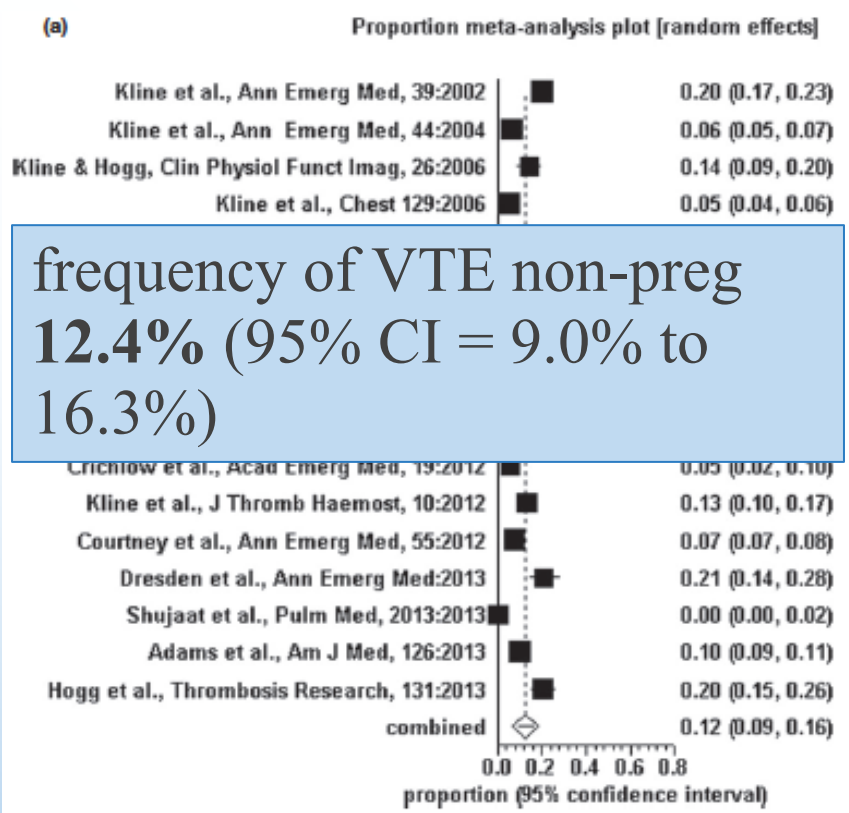
Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

EVIDENCE-BASED DIAGNOSTICS

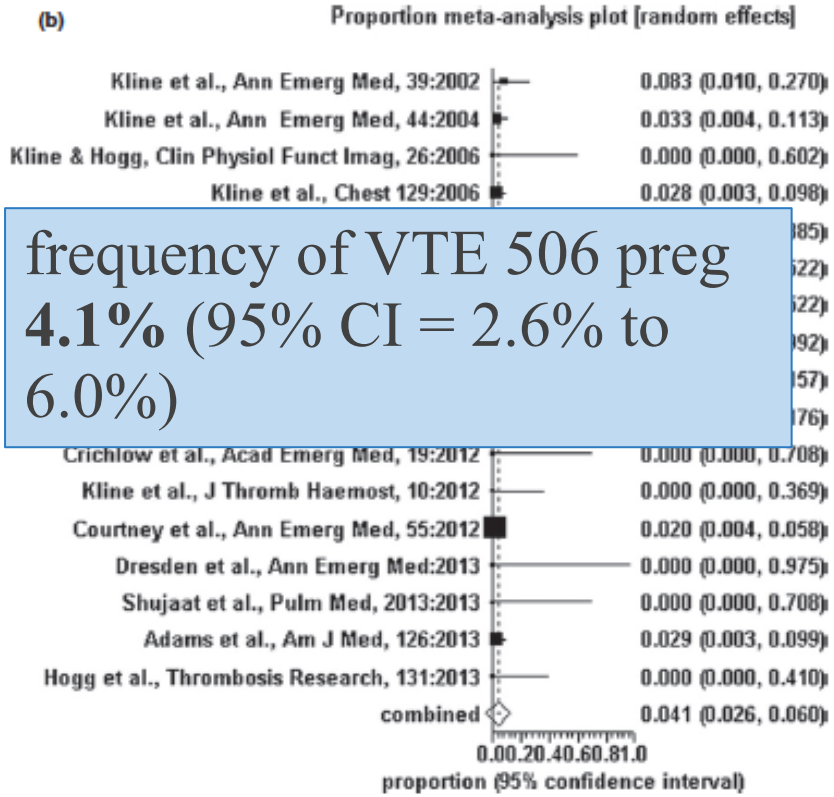
2014;21:949–959

Systematic Review and Meta-analysis of Pregnant Patients Investigated for Suspected Pulmonary Embolism in the Emergency Department

Jeffrey A. Kline, MD, Danielle M. Richardson, Martin P. Than, MBBS, Andrea Penaloza, MD, PhD, and Pierre-Marie Roy, MD



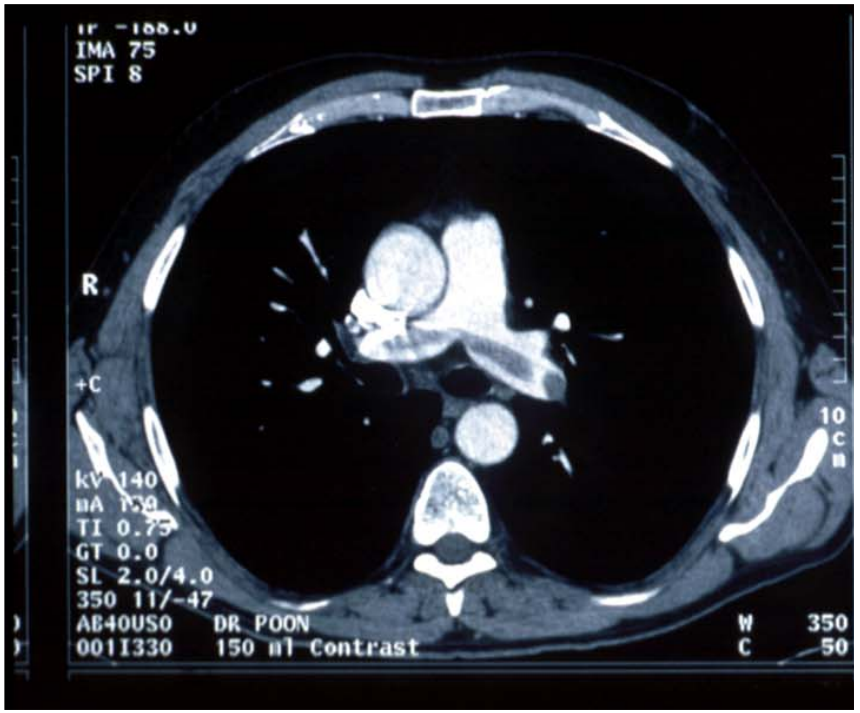
frequency of VTE non-preg **12.4%** (95% CI = 9.0% to 16.3%)



frequency of VTE 506 preg **4.1%** (95% CI = 2.6% to 6.0%)

Radiation exposure

	Rads	mGy
CXR	<0.001	<0.01
Perfusion scan	<0.08	<0.8
Ventilation scan	<0.01	<0.1
CTPA / Helical CT	<0.013	<0.13
Max recommended	<0.5	5



V/Q versus CTPA

Increased risk of fatal childhood cancer to the age of 15 following in utero radiation exposure = 0.006% per mGy, (1 in 17 000 per mGy).

The fetal radiation exposure associated with CTPA = 0.1 mGy

V/Q = 0.5 mGy

- 10 mGy radiation (CTPA) to a woman's breast increases lifetime risk of developing breast cancer by 13.6% above her background risk

- V/Q investigation of first choice for young women especially if FH of breast CA or patient has had previous chest CT scan
- Higher rate of nondiagnostic scans in pregnancy with CTPA (37.5%)

V/Q (4%)

(may be related to the imaging protocol employed).

Ridge CA, et al. Am J Roentgenol 2009;193:1223–7.

CTPA vs V/Q

304 women with a clinical suspicion of PE

Primary outcome =

nondiagnostic study for PE (CTPA)

"low or intermediate probability" in the V/Q group.

initial diagnostic test = CTPA in 108 (35.1%)

V/Q in 196 (64.9%)

Higher rate of nondiagnostic study CTPA (17.0% compared with 13.2%, P=.38)

subgroup of women with a normal chest X-ray,

CTPA more likely to yield a nondiagnostic result than V/Q even after adjusting

30.0% cf 5.6%, adj OR = 5.4, 95% CI 1.4-20.1, P<.01).

Cahill AG et al. Obstet Gynecol. 2009 Jul;114(1):124-9

Case 2

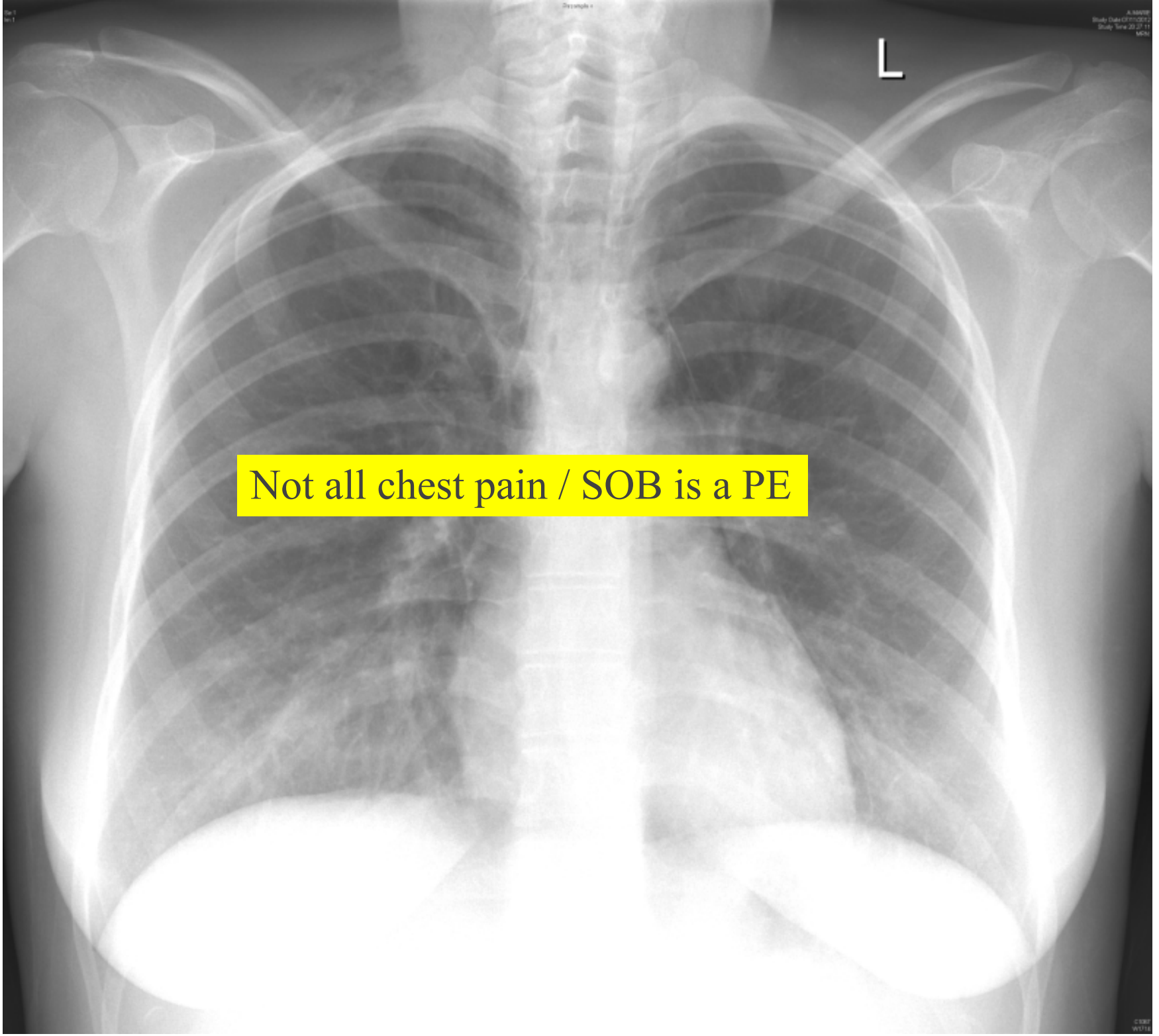
35 year old

1 day post first normal vaginal delivery

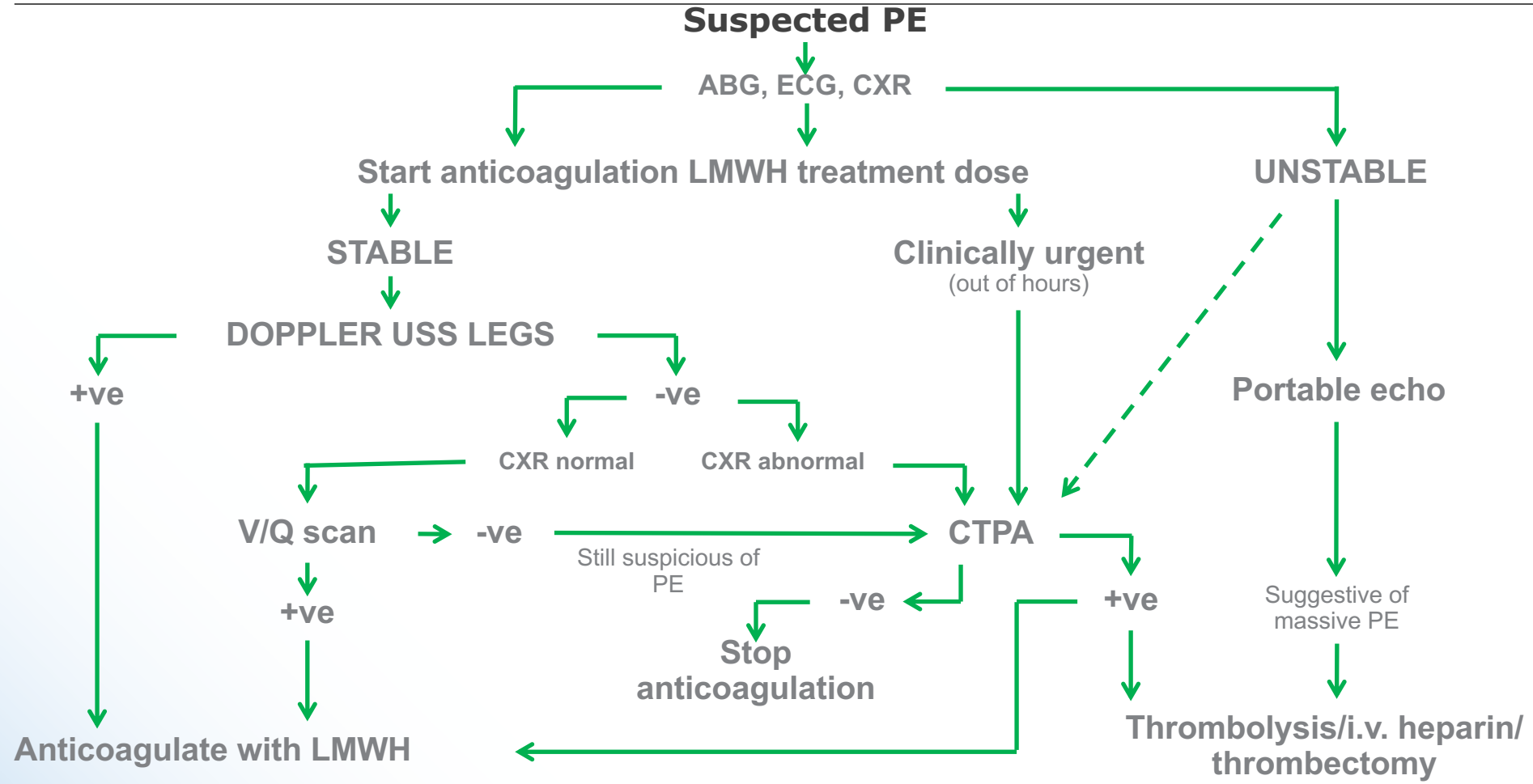
C/O chest pain

Obstetric SHO requests CTPA

Medical registrar asked to review - told CXR normal


L
Not all chest pain / SOB is a PE

Diagnostic algorithm for PE in pregnancy



ABG, arterial blood gas;
ECG, electrocardiogram;
CXR, Chest X-ray;
USS, ultrasound sonography;
CTPA, computerised tomography pulmonary angiography

Modified from: Scarsbrook *et al*. *Clin Radiol* 2006;61:1–12

Diagnosis of PE in pregnancy

Women with suspected PE should be advised that, **compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small.**

Recent studies have shown a **superior sensitivity and specificity when using V/Q single photon emission computed tomography (SPECT) in diagnosing PE than conventional planar V/Q scintigraphy** and this may safely be performed in pregnancy.

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b

April 2015

6.2 What is the therapeutic dose of LMWH in pregnancy?

LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. [C]

There should be clear local guidelines for the dosage of LMWH to be used. [GPP]

Treatment: Dose of LMWH

Give while waiting for confirmation

Enoxaparin 1mg/kg/bd

1.5 mg/kg od (= non-pregnant dose)

Higher doses of **dalteparin** also recommended

Usual dose of **tinzaparin** 175 u/kg/day

LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. [*New 2015*] C

Thrombolysis

For massive (and sub-massive) life threatening PE with haemodynamic compromise

Systematic review - 29 articles, 189 patients

No maternal deaths

1.6% major bleeding events in largest series (122 pts)

67 other pts

- 3 major, 2 minor bleeding events,
  3 fetal deaths

Ahearn et al. Arch Int Med 2002
Eric J Gartman. Obstetric Medicine 2013;6:105-111

Role of IVC filters

Consideration should be given to the use of a temporary inferior vena cava filter in the peripartum period for patients with iliac vein VTE to reduce the risk of PE or in patients with proven DVT and who have recurrent PE despite adequate anticoagulation. D

Intrapartum management

Treat for as long as possible before delivery

Liaise with obstetric anaesthetist

OK to interrupt LMWH for 24hrs if > 2/52 Rx

Consider siting epidural at this time

? Convert to UH

No place for a caval filter

IVC filters

JAMA Intern Med.
Published online March 18, 2013.
doi:10.1001/jamainternmed.2013.343

ONLINE FIRST

Indications, Complications, and Management of Inferior Vena Cava Filters

The Experience in 952 Patients at an Academic Hospital With a Level I Trauma Center

Shayna Sarosiek, MD; Mark Crowther, MD; J. Mark Sloan, MD

Conclusion and Relevance: Our research suggests that the use of IVC filters for prophylaxis and treatment of venous thrombotic events, combined with a low retrieval rate and inconsistent use of anticoagulant therapy, results in suboptimal outcomes due to high rates of venous thromboembolism.

Post partum management acute VTE

Drop dose to 1.5 mg/kg/day

Continue LMWH for 6 weeks

Switch to warfarin > 5 days post delivery

Don’t use DOACs

Contraceptive issues

Lessons form MBRRACE: Root cause / swiss cheese

Delayed dose

Missed dose

Delayed review

Inadequate review

Following caesarean delivery in an obese parous woman the first dose of LMWH was delayed for 18 hours and a further dose was omitted during her postnatal stay.

In the second postnatal week when she was still in hospital she complained of shortness of breath and feeling unwell. There was a delay obtaining medical review and when found to be tachycardic with an abnormal ECG the only investigation planned was a full blood count. She collapsed a few hours later having become more tachycardic and had a cardiac arrest while awaiting transfer to an acute hospital.

Deaths in first trimester

- *Two women with risk factors presented to the emergency department*

one with leg pain:

- *D dimers over 20 fold upper limit of normal.*
- *A negative leg Doppler was assumed to exclude a DVT despite clinical suspicion and a very high D dimer.*
- *Further presentations to the GP with leg pain did not prompt a re-evaluation of the possibility of DVT.*
- *When a DVT was finally diagnosed an inadequate treatment dose of LMWH was prescribed.*

one woman, referred by the GP with suspected PE:

- *Diagnosis of chest infection was made despite a clear chest on examination and very abnormal D dimer.*
- *chest x-ray was not performed with a comment that unless necessary it should be withheld because of the pregnancy.*
- *Obstetric team were not informed despite the GP having alerted them to the woman's referral and the suspected diagnosis.*

Learning points

- Even though D dimer measurement is not routinely recommended in pregnancy, if it is measured, a very high level should not be attributed solely to pregnancy especially in the first trimester/early pregnancy.
- Furthermore the negative predictive value of D-dimer is not sufficient to exclude DVT with a negative result in pregnancy.


Beware of Blood Clots!
Did you know that blood clots are more common in the first few weeks after giving birth?
Stop the Clot!
Have you asked about your anti-clot injection?
Check with your midwife or with your doctor whether you need one.
Thrombosis Charity