

Air travel, thrombosis & early pregnancy

Mike Greaves
University of Aberdeen



Air travel, thrombosis & early pregnancy

- Epidemiology of VTE
- VTE and pregnancy
- Link to travel
- Levels of relative and absolute risk
- Mechanisms
- What to do?

Epidemiology and Natural History of VTE

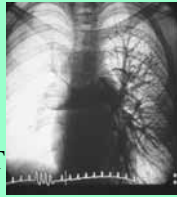
Venous Thromboembolism

- DVT 1:1000 per annum
- PE 1:3000 – 5000 per annum
- DVT in women < 30yr 1:10,000 per annum



Natural History of DVT

- Majority arise in calf veins
- 80% proximal at presentation
- Distal DVT unlikely to embolise
- Asymptomatic PE in 30-50% DVT presentations



Thromboembolism



Post-phlebotic syndrome

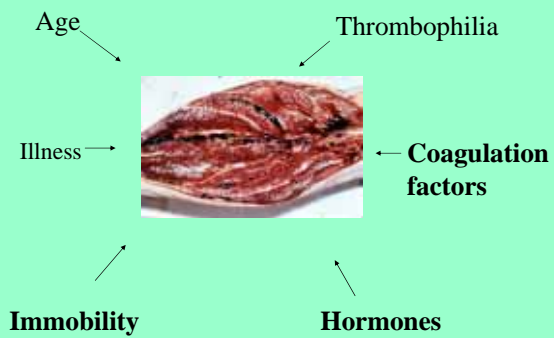
- In up to 30%
- Leg ulcers in 2-10% at 10 years

Prandoni et al, Ann Int Med. 1996, 125:1



VTE and Pregnancy

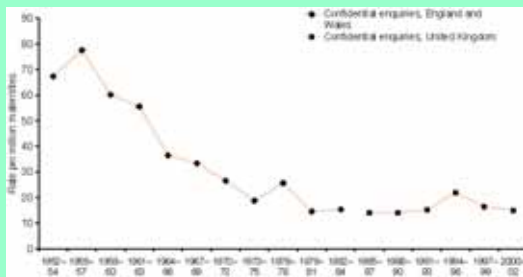
Pathogenesis of VTE



VTE and pregnancy

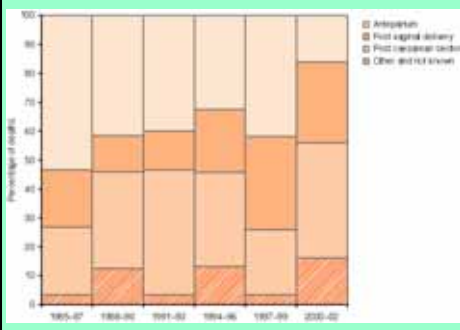
- Increased blood coagulability
- Reduced systemic fibrinolysis
- Hyperemesis
- Relative immobility
- Pressure effects from gravid uterus

Confidential Enquiry 2004



2000-2: 25 deaths from pulmonary embolism

Confidential Enquiry 2004



3: 1st trimester

1: 3rd trimester

3: after fetal loss

18: post-partum

[10: post-CS]

Confidential Enquiry 2004

- 19 of 25 had identifiable risk factors [6: no information]
- 3 of 4 antenatal had history of DVT
- 9 of 25 were obese
- **2 [antenatal] of 25 had undertaken a long journey, 1 by air and 1 by car**
- Substandard care in 57%

VTE: The Link to Air Travel

DVT and immobility

- Air raid shelters: Simpson 1940
- Confined seating in cars and planes: Homans 1954
- 'Economy class syndrome': Cruickshank et al 1988

Frequency and prevention of symptomless DVT in long haul flights : randomised trial.
Scurr et al Lancet 2001, 357:1485

- 479 volunteer flyers
- >8 hour flight in economy class
- Randomised to compression stockings
- Investigations:
 - Calf ultrasound

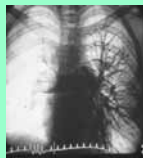
Frequency and prevention of symptomless DVT in long haul flights : randomised trial.

- 12/116 with no stockings had DVT
- 0/115 with stockings had DVT

Scurr et al

Severe PE and air travel

Lapostolle et al N Eng J Med 2001, 345:780-3



- Charles de Gaulle airport [1993-2000: 135.3x 10⁶ passengers]
- Included survivors with PE on arrival
- Analysed:
 - Distance travelled
 - Risk factors for VTE

Severe PE and air travel

- 170 admitted
- 56 (33%) confirmed PE 42(75%) F
14(25%) M
- 42(75%) Economy class
- 2(4%) Business class

Lapostolle et al 2001

Mobility

- 3 (5%) reported leaving their seat
- **42 (75%) reported never leaving seat**
- 11 (20%) unknown

Lapostolle et al 2001

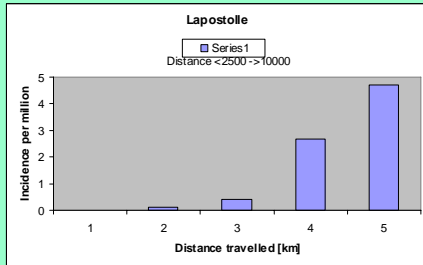
Lapostolle et al 2001

Risk factors for severe PE

Varicose veins	14
OCP or HRT	18
Age >40	49
Obesity	5
Tobacco	4

Total 49

Incidence of severe PE /million passengers
as a function of distance travelled



Lapostolle et al 2001

Deep vein thrombosis and air travel: Record
linkage study

Kelman et al, BMJ, 2003, 327:1072-80

- n=5408 patients with VTE, 1981-99
- Matched with international flight arrivals
- 153 Australians admitted with VTE within 100 days of travel
- 46 within 14 days

Deep vein thrombosis and air travel: Record
linkage study

Kelman et al, BMJ, 2003, 327:1072-80

RR 4.2 [2.9-5.4]

7.3 additional
VTE/million
arrivals

1 long haul
flight/ yr
increases risk by
12%

Role of additional risk factors

Martinelli et al Arch Int Med 2003, 163:2674-6

- Case control study, n=210/210
- Air travel in the month preceding VTE
- OR for air travel 2.1 [1.1-4.0]
- Air travel + thrombophilia 16.1 [3.6-71]
- Air travel + OC 13.9 [1.7-117]

MEGA Study

Cannegieter et al PLoS Med 2006 August 22 [epub]

- Case control design
 - 1,906 patients with first VTE
 - OR 2.1 [1.5-3.0] **Any form of travel**

 - Factor V Leiden OR 8.1
 - Oral contraceptive OR > 20
 - >1.9m tall OR 4.7
 - <1.6 m tall OR 4.9 [air travel only]
- Synergy more prominent with air travel

Absolute risk

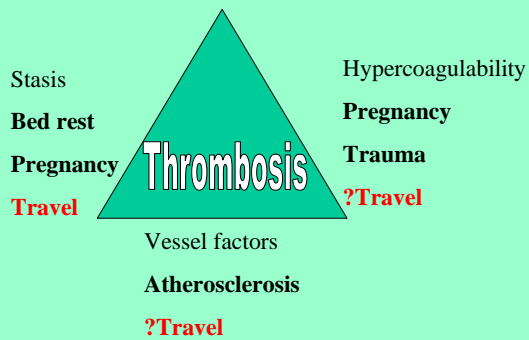
- Questionnaire based study of employees of international companies
- Event within 4 weeks
- n=86,748 flights of >4 hours
- **Absolute risk 1/5944** [1/3,433-12,714]
- Higher if multiple flights
- 1/1000 if flight >12 hours

Conclusions

- Air and other travel predisposes to VTE
- **Absolute risk is around 1 in several thousands for symptomatic VTE**
- Travel duration is a factor
- Main risk period around 2 weeks
- Death is extremely uncommon
- Additional risk factors are often present

Air Travel and Thrombosis: Mechanisms

Virchow's Triad



Possible Mechanisms

- Dehydration
- Excessive alcohol
- Poor air quality
- Immobility
- Hypobaric hypoxia
- Sedatives

Hypobaric chamber

- 6 -8 volunteers at a time
- 40ml blood taken before boarding 8-9am "take-off"
- and within 20min of "landing" at 4-5pm



Study Population

Group I (low risk)

49 healthy volunteers (27 M) aged 18-40 years
no known risk factors

Group II (intermediate risk)

- (a) 12 healthy volunteers ≥ 50 years (4M)
- (b) 12 healthy females 18-40 years using combined OC

Exposed for 8h each to
NN = normobaric normoxic (sea level) or
HH = hypobaric hypoxic (altitude of 8000 feet)
1 -2 weeks apart

Laboratory Tests

- Thrombin and Fibrin Generation
 - Factor VIIc/VIIa
 - Factor VIIIc
 - Thrombin antithrombin (TAT)
 - F1+2 peptide
 - Fibrin monomer
 - EndogenousThrombinPotential
 - TFPI
- Fibrinolysis
 - D-dimer (Vidas)
 - PAI-1
 - Plasmin-antiplasmin
 - t-PA

Laboratory tests, continued

- Endothelial cell function/damage
 - Von Willebrand factor
 - Soluble E-selectin
 - Soluble thrombomodulin
 - Soluble P-selectin
- Platelet activation and adhesion
 - Beta-thromboglobulin
 - Platelet fibrinogen binding with ADP and TRAP
 - Platelet-leukocyte conjugates
- Blood cells
 - Full blood count, haematocrit

Summary

- No significant differences between mean changes in normobaric/normoxic vs. hypobaric/hypoxic conditions in young healthy subjects

Conclusions

In healthy subjects, exposure to mild hypobaric hypoxia is not associated with prothrombotic alterations in haemostatic parameters and is unlikely to be a contributory factor in the aetiology of air-travel related VTE in most subjects

Toff et al JAMA 2006, 295:2297-9

An in-flight study

Schreijer et al, Lancet 2006, 367:832-8

- Some evidence for increased coagulation activation after flying compared with sitting at sea level/normal activities
- Most marked in OCP users with factor V Leiden

What to do?

Guidance in pregnancy [RCOG 2001]

	Short	Long [>3 h]
No risk factors	Exercise/Hydration	+ Elastic Compression

High risk	As for long	All plus LMWH for two days
------------------	-------------	----------------------------

- >100 kg
- BMI >30
- Multiple pregnancy
- Thrombophilia
- Family history
- Medical disorders

A survey of advice given

Voss et al J Obstet Gynaecol 2004, 24:859-62

- Aspirin 53%
- Stockings 49%
- Heparin 4%

- Only in 2nd and 3rd trimester 44%

Evidence for aspirin/LMWH in asymptomatic VTE

Cesarone et al Angiol. 2002, 53:1

- Randomised study in high risk fliers
- DVT incidence:
 - No treatment 4/82
 - Aspirin 3/84
 - LMWH 0/82

Conclusion

- The risk of VTE is increased in pregnancy
- The absolute risk of **travel**-related VTE is low, including in pregnancy
- Avoidance of stasis and maintenance of hydration are reasonable interventions
- Use of LMWH could be considered in exceptional cases
