

Venous Thromboembolism: Women at risk: Who, When and Why?

Dr Julia A M Anderson

Consultant Haematologist

Department of Clinical and Laboratory Haematology
Royal Infirmary of Edinburgh

Estimated Annual Incidence of VTE

- Estimated annual incidence of VTE is
117/100,000 persons
 - 48/100,000 for DVT
 - 59/100,000 for PE
 - sudden death in 1-2% patients
 - significant morbidity from post-thrombotic syndrome



Incidence rates of VTE rise dramatically at age 55yrs

3098 SILVERSTEIN et al

BLOOD, 1 NOVEMBER 2007 • VOLUME 110, NUMBER 9

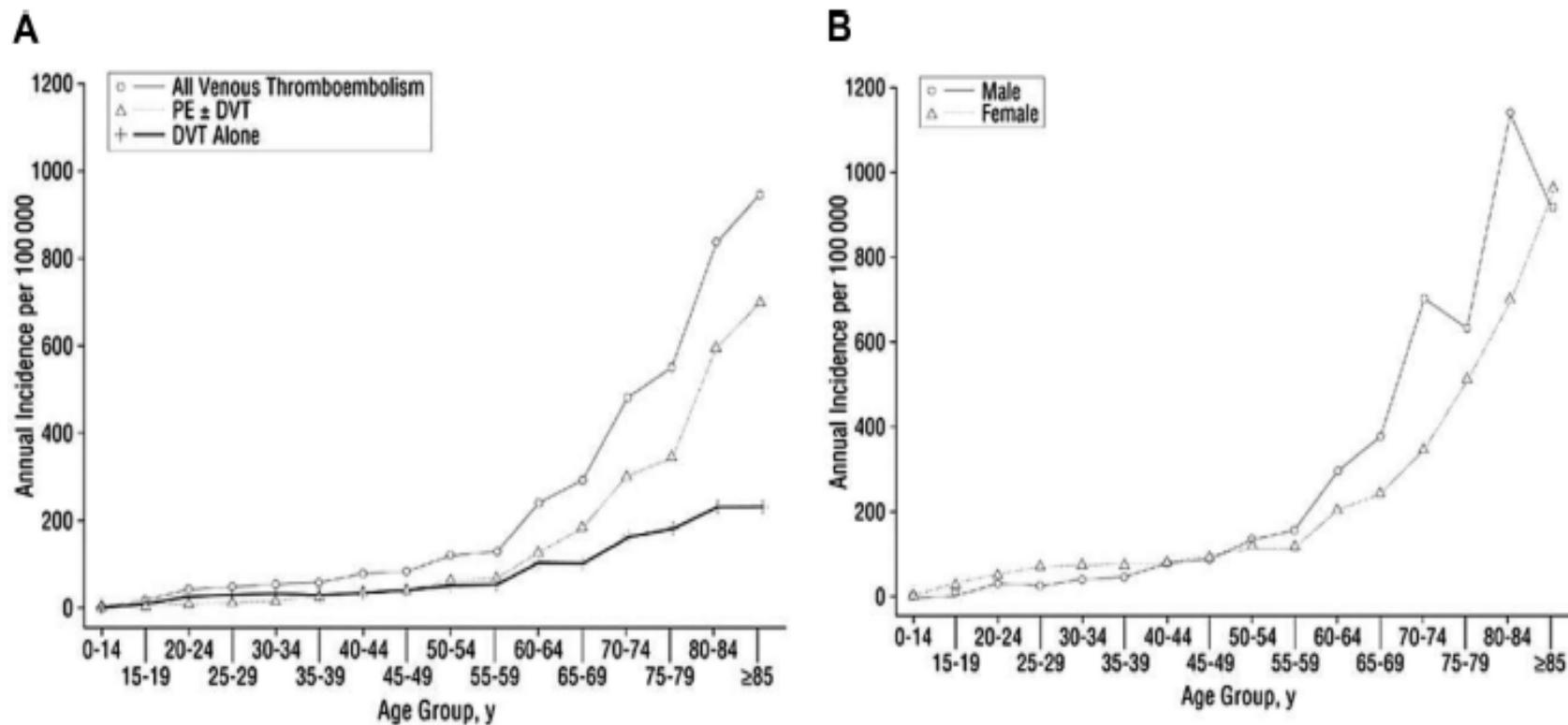
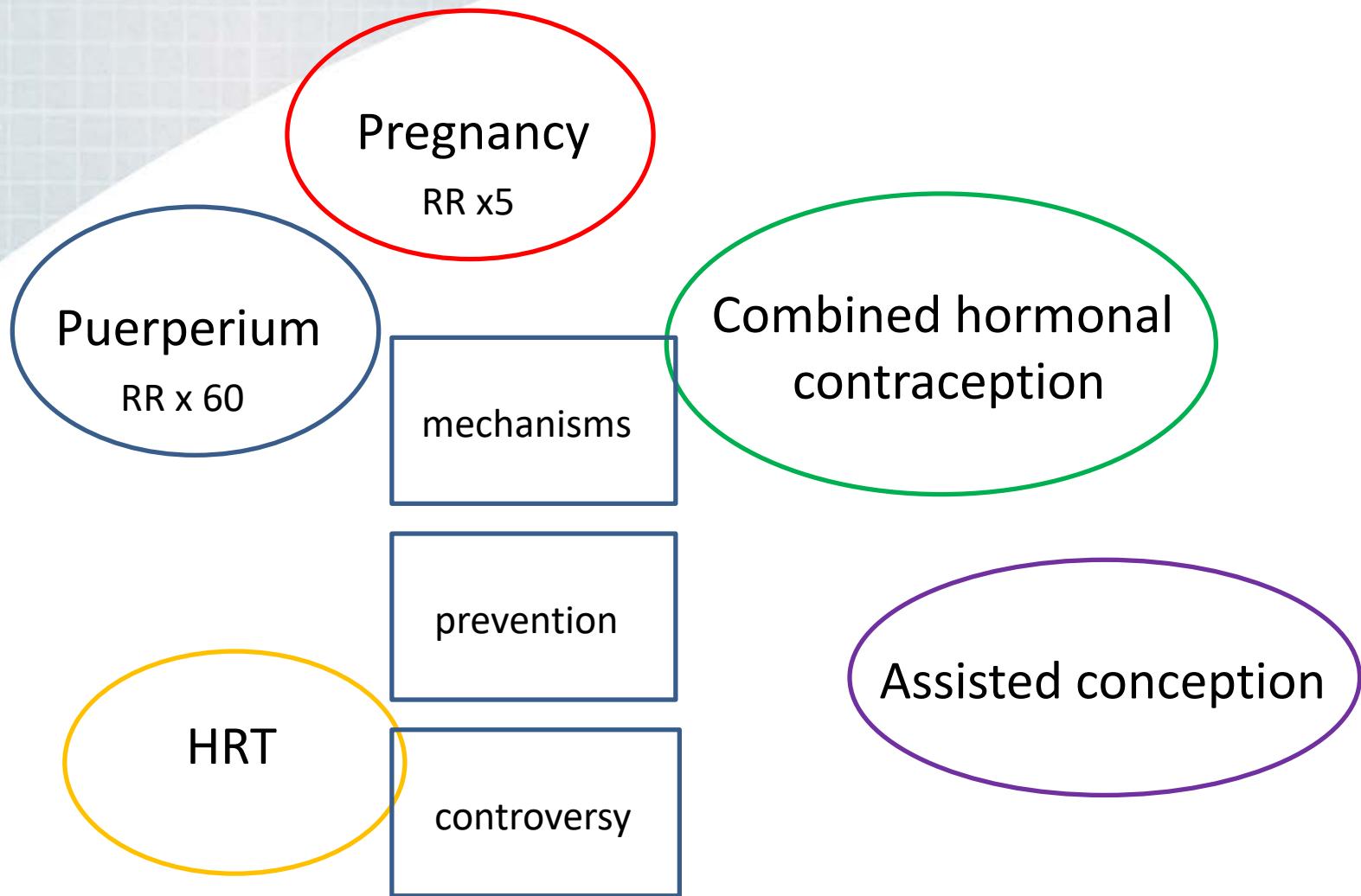


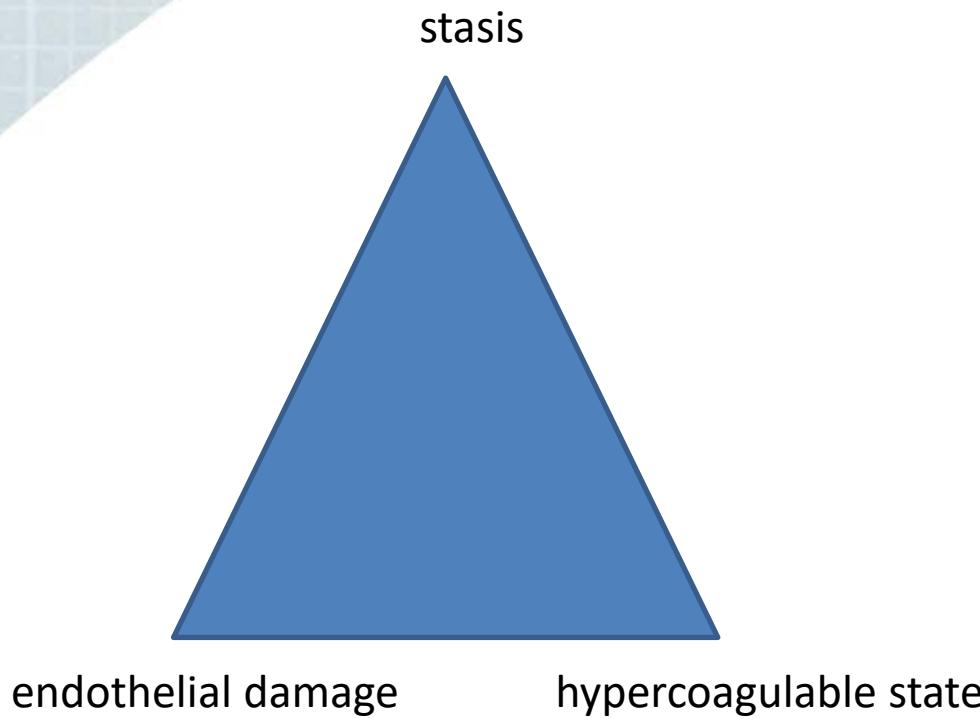
Figure 1. Annual incidence of venous thromboembolism among residents of Olmsted County, Minnesota, from 1966 to 1990. (A) All VTE, deep vein thrombosis (DVT) alone, and pulmonary embolism (PE) with or without deep vein thrombosis (PE ± DVT) by age. (B) All VTE by age and sex. Reproduced with permission.⁶

VTE: a “reproductive health risk”



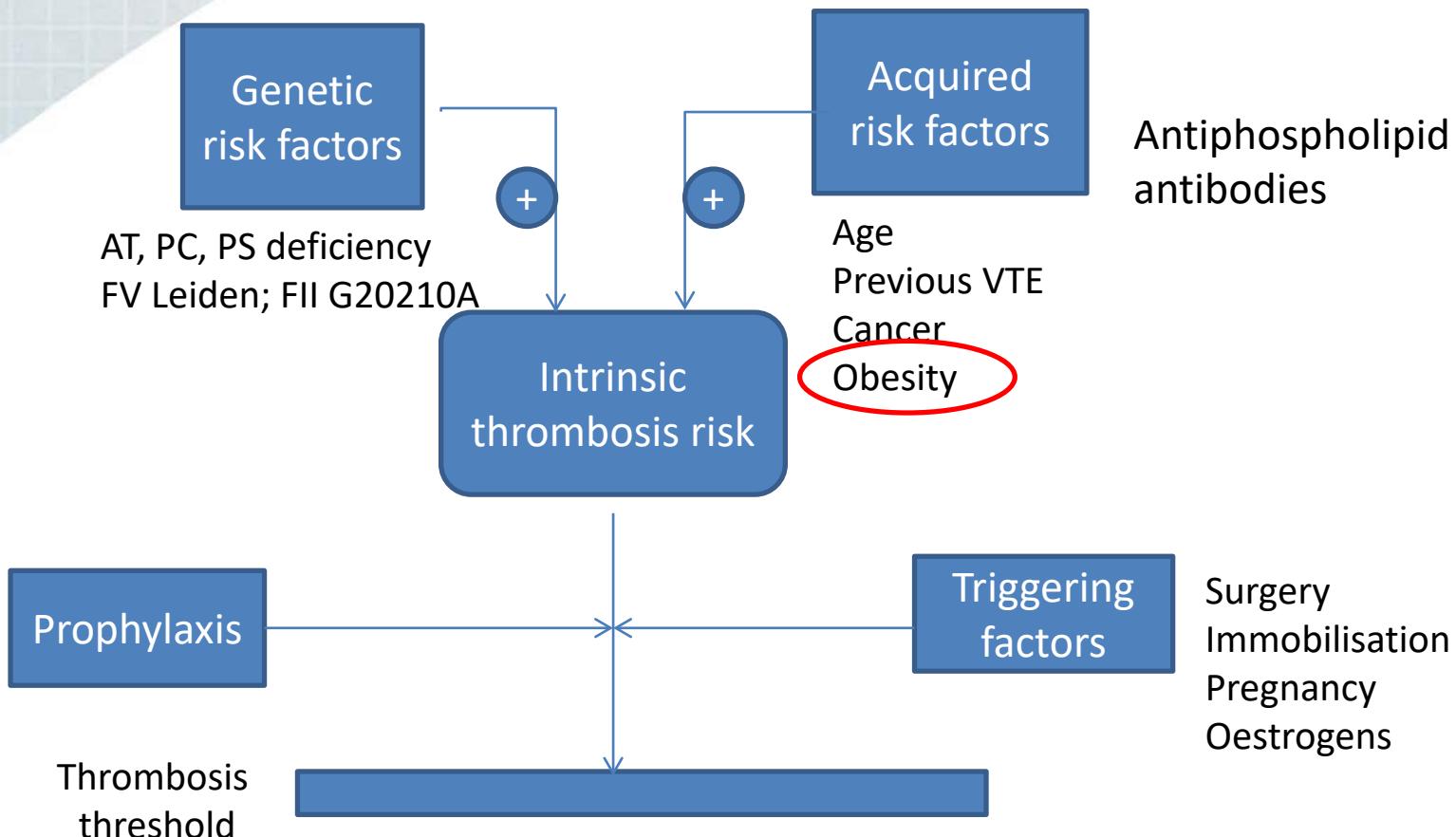


Virchow's Triad



Rudolf Virchow, 1821-1902

THROMBOSIS THRESHOLD



Obesity

- Obesity predisposes to venous stasis, increases prothrombotic factors and impairs fibrinolytic activity.
 - Obesity is an independent risk factor for venous thrombosis, rather than simply being associated with immobility
- In the UK Confidential Enquiry into maternal deaths, 18 women died from VTE in the triennium 2006–2008.
 - Obesity was identified as the most important risk factor.
 - 14 women were overweight ($BMI \geq 25 \text{ kg/m}^2$), of whom 11 had a $BMI \geq 30$, including 3 who had a BMI of ≥ 40 (CMACE, 2011).

Allman-Farinelli MA. Obesity and thrombosis: a review. Semin Thromb Hemost 2011; 8 : 903-907.

CMACE Centre for Maternal and Child Enquiries. Saving mothers' lives. Reviewing maternal deaths to make motherhood safer. 2006-2008. BJOG 2011; 118 (Suppl 1) : 1-205.

Classification of Heritable Hypercoagulable States

Hereditary	Prevalence (%)	Relative risk of first venous thrombosis
<u>Loss of function</u> Antithrombin deficiency - mutation in SERPINC1 gene	0.02	5-10
Protein C deficiency - mutation in PROC gene	0.2	4-6.5
Protein S deficiency - mutation in PROS1 gene	0.03- 0.13	1-10
<u>Gain of function</u> Factor V Leiden (FV R506Q)	3.0-7.0	3-5
Prothrombin (F2 G20210A)	0.7-4.0	2-3
Elevated FVIII, IX, XI, VII	10	2-5



Combined Hormonal Contraception (CHCs)

- CHCs cause:
 - increases in procoagulant coagulation factors
 - reduced levels of natural anticoagulant proteins (protein S and tissue factor pathway inhibitor)
 - changes in fibrinolytic parameters
- Long recognition that use of CHC associated with an excess risk of VTE
 - In 1960's, on the basis of UK, Swedish and Danish data, excess risk attributed to the oestrogen dose of various CHCs
 - Led to reduction in oestrogen doses in late 1960's and early 1970's

Combined Hormonal Contraception (CHCs)

- Thrombotic risk differs dependent on the doses of oestrogen and progestogen in the pill.
 - second generation progestogens [levonorgestrel (LNG) and norethisterone] regarded as safer than the newer progestogens. (subject of an ongoing debate)
- Highest risk in obese, smokers and those with underlying thrombophilia:-

Associated factor	RR
PC, PS, AT	High
Factor V Leiden	20-30
Prothrombin 20210A mutation	10-20
High procoagulant factor levels	5-10
Obesity	24
Smoking	9

Emerging evidence that patients with polycystic ovarian disease might have a higher risk

Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis

E Van Vlijmen et al. 2016, JTH 14 1393-1403.

- Dutch group performed a meta-analysis on VTE risk in thrombophilic CHC-users.
 - 12 case-control studies; 3 cohort studies
 - the absolute VTE risk higher in CHC-users with severe thrombophilia than mild thrombophilia (4.3-4.7 vs 0.49-2.0 per 100-pill years)
 - the results support discouraging CHC-use in women with a natural anticoagulant deficiency.
 - but, the additive risk of factor V Leiden (FVL) or prothrombin-G20210A (PT) mutation is modest.
- Authors suggest that women with a FVL/PT-mutation **as single risk factor** can use CHCs if alternatives are not tolerated.

Communication Models when Delivering Counselling

Effect of information on the perception of users and prospective users of combined oral contraceptives regarding the risk of venous thromboembolism

Machado et al. Gynecol. Endocrinol. 2015: 31(1):57-60

- A cross-sectional study of 159 users or potential users of CHCs
- Evaluated patient knowledge (self-administered questionnaire) on the risk of VTE associated with CHC and perception of risk depending on presentation as a relative risk (RR), an absolute risk (AR) or an attributable risk (AtR)
- 67.9% expressed concern if the risk was presented as RR
- 14.5% and 10.7% expressed concern if the risk presented as AbR or AR, respectively
- Important when counselling patients for CHC initiation

Importance of good contraceptive advice for women of childbearing potential taking DOACs

- Recent guidance from the Scientific and Standardization Committee (SSC) of The International Society on Thrombosis and Haemostasis (ISTH)
- Following recommendations:
 - Give robust counselling on avoidance of pregnancy prior to commencing DOAC treatment
 - Switch from a DOAC to LMWH or warfarin when planning a pregnancy
 - Immediate change to LMWH on confirmation of unintentional pregnancy
 - Current evidence suggest that inadvertent exposure is not grounds for termination, but non-directional counselling, early review and foetal monitoring should be carried out
 - Avoid breast-feeding due to lack of evidence of safety
 - Collect and report data in pregnancy and outcomes to improve knowledge on potential harms;
 - Report all cases to the ISTH registry

Pregnancy and Puerperium

- VTE occurs in 1–2 per 1000 pregnant women every year
 - PE is considered one of the main causes of maternal mortality in Western countries
 - Pregnancy-related DVT is one of the main causes of maternal morbidity
 - major determinants : advanced age, parity, mode of delivery and systemic risk factors (such as co-morbidities)



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Pregnancy

- Normal pregnancy is associated with a hypercoagulable state in preparation for the haemostatic challenges of delivery
 - Venous stasis due to progesterone-induced venodilatation, pelvic compression by the gravid uterus, pulsatile compression of left iliac vein by right iliac artery
 - Levels of factors V, VII, VIII, IX, X, XII and von Willebrand antigen increase, and protein S, factor XI and platelets tend to decrease throughout pregnancy along with acquired resistance to protein C
 - Leads to increased thrombin generation (evidenced by rise in D-dimers and prothrombin fragments 1+2) and reduced fibrinolysis

Puerperium

- PE is more prevalent in the puerperium
 - Haemoconcentration
 - Dissemination of tissue factor in the bloodstream after placenta removal
 - Caesarean section

Thromboprophylaxis in pregnancy

- Low-molecular-weight heparin (LMWH) given subcutaneously once daily is the drug of choice for preventing pregnancy-related VTE
- Optimal dose of LMWH for VTE prophylaxis in pregnancy is not established
 - doses range from 2000 to 4000 units or more
Lindqvist & Hellgren, JTH 2011: 9; 1669-1670
- LMWH is safe for the foetus: does not cross the placenta
 - while vitamin-K antagonists (e.g. warfarin) are associated with foetal abnormalities if taken weeks 6-11 and in third trimester
 - handling of DOACs is uncertain

Thromboprophylaxis in pregnancy who??

- “**primary**”: prevention of a first VTE in women considered at risk
- “**secondary**”: aimed to prevent VTE recurrence
 - Women with severe thrombophilia due to antithrombin, protein C or protein S deficiencies, homozygous for factor V Leiden or prothrombin mutation, antiphospholipid antibodies and combined abnormalities merit primary prophylaxis
(Martinelli et al., *Thr Haemost* 2002, 87: 791)
 - Women with the more common heterozygous FVL or prothrombin mutations have a small increased risk of pregnancy-related VTE and should be counselled about signs and symptoms of VTE without prescribing LMWH through the gestational period
(Rodger et al. TIPPS study. *Lancet* 2014:1673-83)

Thromboprophylaxis in pregnancy

- Other risk factors to be taken into account when deciding the appropriateness of antithrombotic prophylaxis during pregnancy
 - family history of VTE, the presence of co-morbidities, obesity and maternal age
 - how much weight should be placed on additive risk factors?
- In the puerperium women with any type of thrombophilia should receive LMWH prophylaxis.

Secondary thromboprophylaxis in pregnancy

- If the previous thromboembolism was
 - idiopathic
 - pregnancy-related
 - occurred during CHC usethe risk of recurrence in pregnancy is higher than if the VTE was surgery- or trauma related.
 - Women with previous VTE occurring after surgery, leg fracture or immobilisation (e.g. plaster cast) may avoid LMWH prophylaxis in pregnancy.
- In the puerperium, all women with previous VTE should receive LMWH prophylaxis



Assisted conception and VTE

- Ovarian stimulation increases the risk of thromboembolic disorders
 - Down-regulation or use of oestrogen for endometrial preparation prior to embryo transfer
- Risk seems greatest in pregnant women with ovarian hyperstimulation syndrome (OHSS) requiring hospital admission with estimated risk of ~ 2% (Rova et al., Fertil Steril 2012;97: 95-100)
- Various case reports demonstrate that:
 - both the arterial and the venous systems may be affected
 - VTE can occur up to several weeks after embryo-transfer
 - these events are more common in women who conceive in the presence of OHSS (Chan, Curr Opin Obstet Gynecol 2009, 21: 207)
 - the events tend to occur in unusual locations (the upper extremities and the neck for venous thrombosis and intra-cranially for arterial events)

Assisted conception and VTE

- All women undergoing IVF should undergo an individual risk assessment taking into account previous VTE, family history, concurrent medical conditions, age, obesity.
- Women with previous VTE should receive thromboprophylaxis
(Nelson, Thr Res 2009, 123: 9 Suppl 3 S8)
- Thromboprophylaxis with LMWH until the 13th week of gestation is suitable for women conceiving in the presence of OHSS.
 - An alternative approach is to consider postponing embryo transfer in women at consistent risk of developing OHSS
D'Angelo, Semin Repro Med 2010, 28: 513
 - Cryopreserved oocytes or embryos can be safely used in a subsequent unstimulated cycle.
- Screening for thrombophilia is unlikely to be cost-effective.

Menopause and HRT

- Menopause is associated with increased coagulation factor levels and alterations of platelets and fibrinolysis
- HRT is associated with a 2- to 4-fold increased risk of DVT
Rosendaal et al. JTH 2003, 1: 371
- The thrombotic risk depends on the route of oestrogen administration
 - odds ratio for VTE in users of oral and transdermal oestrogens compared with non-users is 3.5 (95% CI: 1.8–6.8) and 0.9 (95% CI: 0.5–1.6), respectively
- HRT should only be prescribed for the relief of serious menopausal symptoms (The Writing Group for the Women's Health Initiative, 2002)

Summary

- VTE is a serious health problem for both men and women but, because of pregnancy and common hormonal treatments, it **is a specific health risk for women.**
- Clinicians managing pregnant women or treating them for infertility or with oral contraceptives or HRT should be aware of the **need to take a careful medical history to identify additional co-existing risks.**