

# Thrombosis and thrombophilia in pregnancy

Scott Dunkley

# Case 1

- 30yro lady
  - Returns from honeymoon OS pregnant and distal DVT
1. Continue anticoagulation full dose throughout entire pregnancy
  2. Reduce to prophylactic dose after 3mths
  3. Recommence prophylaxis postpartum ?

# Case 2

- 28yro 8 weeks pregnant
  - Had IVF
  - Extensive upper extremity DVT
  - Full dose LMWH
1. Mode of delivery
  2. Anticoagulation plan
  3. contraception

## Case 3

- 25yro with FVL, OCP and DVT
  - 8 weeks pregnant
1. Commence prophylactic LMWH
  2. Postpartum prophylaxis only
  3. If antenatal when do you start ?
  4. If antenatal treatment anticoagulation plan at term

# Case 4

- 22yro first pregnancy IUGR
  - FVL homozygous – no personal VTE
  - Mother also homozygous FVL – no VTE, no other FHx
  - Pregnant 12 weeks
1. Postpartum prophylactic LMWH
  2. Antenatal prophylactic LMWH
  3. Treatment dose LMWH

# Case 5

- 38yro with recurrent (3) 1<sup>st</sup> trimester fetal loss
  - FVL
1. Should have antenatal LMWH ?
  2. Postpartum prophylaxis ?

## Case 6

- 26yro RF induced MVR on warfarin
1. Can fall pregnant on warfarin ?
  2. Treatment dose LMWH throughout preg.
  3. Change back to warfarin after 1<sup>st</sup> trimester
  4. Can breast feed on warfarin
  5. Can breast feed on LMWH

# Case 7

- 35yro recurrent DVT and APA on longterm warfarin
  - Became pregnant changed to clexane 100mg/d and aspirin
  - 20/40 developed fever and abnormal LFT with thrombocytopenia, normal coags and no fragments, changed to BD clexane and steroids
  - Worsening clinical condition with CT evidence of hepatic and splenic infarcts
1. Plasmapheresis
  2. Elective TOP
  3. Should she ever have another pregnancy

# Physiological changes in pregnancy

- Venous stasis
  - increased venous distensability and capacity due to high oestrogen levels
  - increased plasma volume
  - compression of IVC by gravid uterus

# Physiological changes in pregnancy

- Alterations in coagulation
  - increased coagulation factors (fibrinogen, FV, FVII, FVIII, VWF)
  - Increased PAI 1 and 2 (fibrinolysis)
  - Acquired APCR - increased FV and FVIII
    - reduced free protein S

# VTE in Pregnancy

- RR of VTE x 5-10 (0.6-1.3 per 1000 delivery)
- PE is important cause of death and approx half occur postpartum
- 2/3rds of DVT occur antepartum but risk is constant across all trimesters
- Mode of delivery
  - vaginal 0.08-1.2%
  - C/S 2.2-3.0%
- DVT left leg 85%
- Iliofemoral > calf veins (72% vs 9%)
- PE occurs in 16% of UnRx DVT

# Prophylaxis in women *without* thrombophilia or prior VTE

## 1. Current:

- Age >35 years
- Obesity (BMI >30) pre-pregnancy or early pregnancy
- Parity >4
- Gross varicose veins
- Paraplegia
- Sickle cell disease
- Inflammatory disorders e.g. inflammatory bowel disease
- Some medical disorders e.g. nephrotic syndrome, cardiac disease
- Myeloproliferative disorders

## 2. New onset or transient:

- Surgical procedure in pregnancy or puerperium e.g. LSCS, evacuation of retained products of conception, postpartum sterilisation
- Hyperemesis
- Dehydration
- Ovarian hyperstimulation syndrome
- Severe infection e.g. pyelonephritis
- Immobility (>4 days bedrest)
- Pre-eclampsia
- Excessive blood loss
- Long-haul travel
- Prolonged labour
- Operative instrumental delivery
- Immobility after delivery

If 2 RF's consider 3-5 days postpartum prophylaxis

If 3 or more then 3-5 days postpartum prophylaxis, consider antenatal

# Caesarian section VTE prophylaxis

- The risk of pulmonary embolism is increased by caesarean section compared with vaginal birth (RR 3.8) with the risk of DVT after caesarean section being 1-2%. The most comprehensive guidelines are those of the RCOG.
- **Low risk cases:** require early mobilisation and hydration with the use of compression stockings.
- **Moderate risk cases:** prophylaxis should be considered if single risk factors are present and given for multiple risk factors, along with the use of compression stockings, early mobilisation and hydration.
- **High risk cases:** prophylaxis must be given with leg stockings until 5th postoperative day or fully mobile. Consideration should also be given to 6 weeks LMWH postpartum

# RCOG risk factors for caesarian

## LOW-RISK:

- Elective LSCS with uncomplicated pregnancy and no other risk factors

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## MODERATE-RISK (two of the following):

- Age > 35 years
- Obesity (> 80kg)
- Para 4 or more
- Gross varicose veins
- Current infection
- Pre-eclampsia
- Immobility prior to surgery (> 4 days)
- Major current illness e.g. heart or lung disease, cancer, inflammatory bowel disease, nephrotic syndrome
- Emergency caesarean section in labour

## HIGH-RISK

- 3 or more of the moderate risk factors listed above
- Extended major pelvic or abdominal surgery, e.g. caesarean hysterectomy
- Personal or family history of DVT, PE or thrombophilia, paralysis of lower limbs
- Antiphospholipid antibody or syndrome

# Management of thrombophilia in pregnancy

1. Primary prophylaxis
2. Secondary prophylaxis in prior VTE
3. Secondary prophylaxis in prior pregnancy complications
4. Treatment of acute events

**Risk of pregnancy-associated venous thromboembolism (VTE) in thrombophilic women without prior disease.**

<b>Thrombophilia</b>	<b>Relative Risk of VTE OR (95% CI)</b>	<b>Estimated absolute risk of VTE events per 1000 patients*</b>
FVL (heterozygous)	8.32 (5.44–12.70)	8/1000
PT gene (heterozygous)	6.80 (2.46–18.77)	6/1000
FVL (homozygous)	34.40 (9.86–120.05)	34/1000
PT gene (homozygous)	26.36 (1.24–559.20)	26/1000
Antithrombin deficiency	4.69 (1.30–16.96)	4/1000
Protein C deficiency	4.76 (2.15–10.57)	4/1000
Protein S deficiency	3.19 (1.48–6.88)	3/1000
MTHFR C677T homozygous	0.74 (0.22–2.48)	1/1000
50% of preg related VTE have a thrombophilia		
A study by Battaglioli T et al (JTH 2007, suppl 2) questioned if homozygous state worse than heterozygous		
*Assuming a baseline risk of 1 event per 1000 pregnant patients without a known thrombophilia		
Data are from Robertson et al. Br J Haem 2005.		

# FVL and PT20210

Combined defects may have a higher risk

- VTE in pregnancy: APCR 78% but Factor V Leiden 46%
- risk of “physiological APCR” is unknown
- study by Gerhardt of VTE in pregnancy;

Defect	prevalence	VTE rate	RR
FVL	43.7%	1:500	9.3
PT20210	16.9%	1:200	15.2
Combined	9.3%	4.6:100	107 (NEJM 2000)

# AT deficiency and pregnancy

This retrospective study showed a much higher risk for AT deficiency

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Defect	rate of VTE in pregnancy
AT3	
Type I	1:2.8
Type II	1:42
PC	1:113
FVL	1:437

(McColl M. Thromb Hemost 1997)

## Secondary prophylaxis in APA

- RF's include titre and subtype of ACA, LA positivity, SLE, prior Hx
- treatment reasonable in recurrent VTE
- prophylaxis reasonable for RPL or prior single VTE
- LMWH and low dose aspirin is standard practice

# Secondary prophylaxis in VTE has been shaped by Brill-Edwards trial

- The risk of recurrent VTE in pregnancy is >10%
- Brill-Edwards P, et al (NEJM 2000) 125 pregnant women with prior VTE >3mths ago, anticoagulation given only postpartum for 6/52
- Antepartum rate 2.4%
- Varied on subgroup
  - idiopathic + thrombophilia = 20%
  - ppte RF + thrombophilia = 13%
  - idiopathic + normal = 7.7%
  - ppte RF + normal = 0%

## MJA Guidelines 2001 - Preventing venous thromboembolism (VTE) in pregnant women with established thrombophilias according to estimated pregnancy-related risk of thrombosis

	AT deficiency <i>(very rare)</i>	PC def <i>(rare)</i>	PS def <i>(rare)</i>	FVL* or PGM# homozygous <i>(uncommon)</i>	FVL* or PGM# heterozygous <i>(common)</i>
Personal history of VTE independent of family history	ThA <b>(C<sub>2</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	Negot <b>(C<sub>1</sub>)</b>
Family history of VTE in one or more 1 <sup>st</sup> degree relatives	ThA/PrA <b>(C<sub>3</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	Negot <b>(C<sub>1</sub>)</b>
Family history of VTE in a distant relative	ThA/PrA <b>(C<sub>3</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	Negot <b>(C<sub>1</sub>)</b>	Negot <b>(C<sub>1</sub>)</b>	Nil <b>(C<sub>1</sub>)</b>
No personal or family history of VTE	ThA/PrA <b>(C<sub>3</sub>)</b>	PrA <b>(C<sub>1</sub>)</b>	Nil <b>(C<sub>1</sub>)</b>	Nil <b>(C<sub>1</sub>)</b>	Nil <b>(C<sub>1</sub>)</b>

# Practical prophylaxis in pregnancy

Risk	Previous VTE and/or thrombophilia status	Prophylaxis
Very high	Previous VTE ( $\pm$ thrombophilia) on long-term warfarin	Antenatal high prophylactic or therapeutic dose LMWH and at least six weeks of postnatal warfarin
High	Previous recurrent VTE not on long-term warfarin Previous VTE + thrombophilia/FH Asymptomatic severe thrombophilia (AT deficiency, combined defects, homozygous FVL or PT gene defect)	Antenatal and six weeks postnatal prophylactic LMWH
<b>Moderate</b>	Single previous provoked VTE without thrombophilia FH or other risk factors Asymptomatic thrombophilia (except antithrombin deficiency, combined defects, homozygous FVL or prothrombin gene defect)	Six weeks postnatal prophylactic LMWH +/- antenatal low dose aspirin

# Treatment of acute event

- anticoagulate thru pregnancy and at least 6 weeks postpartum
- lifelong if AT3 and APA
- Probably not for multiple defects, homozygous FVL

# LMWH is standard of care

- enoxaparin 40mg/day prophylaxis and for treatment  
dose 1mg/kg/BD or 1.5mg/kg/day
- better bioavailability than UFH
- doesn't cross placenta
- not teratogenic (cf warfarin)
- not in breast milk (neither is warfarin)
- low rate of osteoporosis
- less HITTS
- 2<sup>nd</sup> trimester ? dose changes thru pregnancy
  - ? monthly antiXa levels
  - 50% dose increase (abstract #1082 ASH 2002)



## MJA guidelines for regional anaesthesia and levels of consensus

- Regional anaesthesia (epidural or spinal block) is contraindicated during anticoagulation therapy because of the increased (although unquantified) risks of spinal haematoma ( $C_1$ ).
- If a regional anaesthetic is desired in women who require anticoagulation therapy, an elective delivery will allow for a planned reduction in dose or a change to intravenous unfractionated heparin (UH) ( $C_1$ ).
- Therapeutic subcutaneous injections of low molecular weight heparins (LMWH) or UH should be ceased at least 24 hours, and preferably 36 hours, before regional anaesthesia (epidural or spinal block) ( $C_1$ ).
- Intravenous UH (used to permit a rapid return of the APTT to normal after cessation of the infusion) should be discontinued at least six hours, and preferably 12 hours, before regional anaesthesia ( $C_1$ ).
- In women receiving prophylactic LMWH, an interval of more than 20 hours from the last dose should allow the placement of a regional block with minimal risk of complications ( $C_2$ ).
- A normal activated partial thromboplastin time (APTT) does not ensure minimal anticoagulant effect of LMWH, and the platelet count should be determined to exclude heparin-induced thrombocytopenia ( $C_2$ ).
- If caesarean section is being undertaken, further doses of LMWH should be delayed for at least four hours after placement of an uncomplicated regional block, and longer if the regional block has been complicated ( $C_1$ ).
- Low-dose LMWH therapy can be continued after delivery if there have been no complications in the siting of the regional block.
- An epidural catheter can be removed 12-20 hours after a prophylactic dose of LMWH, and the next injection should be delayed by at least four hours after removal ( $C_1$ ).
- Women should be closely monitored postpartum for any symptoms or signs of spinal haematoma, in particular for numbness and weakness in the lower limbs, severe back pain, and bladder or bowel incontinence ( $C_1$ ).

## Risk of spinal haematoma with LMWH

- The safety of LMWH with regional anaesthesia is related to strict guidelines regarding timing of LMWH and neuraxial insertion or removal. When higher and twice daily doses are used, there is a higher incidence of spinal haematoma. Recent extensive review of regional anaesthesia in the anticoagulated patient suggested little risk of spinal haematoma associated with this therapy based upon extensive worldwide experience [Horlocker. Regional Anesthesia and Pain Medicine, 2003; 28:172-197.]. Nine published series with low dose subcutaneous heparin totalling over 9000 patients without complication were cited as well as extensive additional experience in Europe and the United States. In addition a review of 19 articles involving in excess of 9000 patients with LMWH thromboprophylaxis in Europe reported only one case of spinal haematoma. The conclusions of this paper were that LMWH is extremely safe provided strict guidelines regarding dosage and timing are adhered to.
- A further review of 14 studies on 440 pregnancies reported no cases of epidural haematoma or haemorrhagic or neurologic complications [Greer et al. Blood. 2005;106:401-407 ].

## RPAH guidelines

- Regional techniques should not be used until at least 12 hours after previous prophylactic dose of LMWH.
- Regional techniques should not be used until at least 24 hours after previous therapeutic or high prophylactic dose of LMWH (e.g. Clexane 1mg/kg bd).
- LMWH should not be given for at least 4 hours after epidural catheter inserted or removed (6 hours if insertion or removal were traumatic) and the catheter should not be removed within 12 hours of most recent injection.
- When using unfractionated heparin (UFH) 6 hours should elapse from the last dose of heparin before catheter removal and 2 hours before the next dose of UFH.
- For those requiring full anticoagulant therapy in pregnancy, reduce the dose of heparin to thromboprophylactic dose on the day prior to induction of labour and continue with this dose during labour (RCOG).

## In practice...

- Problem with epidural risk rather than bleeding
- Change to UFH 5000U BD from 37-38 weeks for spontaneous delivery
- *Or*, Planned induction
- Induction is standard if therapeutic dose and then usually prophylactic dose postpartum unless had been on longterm anticoagulation
- The ability to reduce from treatment to prophylactic dose is unknown and in general full dose is continued throughout pregnancy if VTE developed during preg.
- Warfarin is still considered if prosthetic valve due to risk of valve thrombosis on LMWH

## Recurrent pregnancy loss (RPL) and complications of pregnancy and thrombophilia

- Probably both associated with thrombophilia
- RFL least controversial, IUGR most
- treatment ? RFL > complications preg

**Table 1** Association between various forms of thrombophilia and pregnancy failure and complications

I.A. Family studies					
Thrombophilia defect	Sporadic miscarriage OR (95% BI)	Recurrent miscarriage* OR (95% BI)	Intrauterine fetal death* OR (95% BI)		
Antithrombin, protein C, or protein S deficiency	2.0 (1.2-3.3) [2] 1.3 (0.9-1.7) [3]	2.6 (0.8-8.0) [2]	3.6 (0.5-7.7) [3]		
Factor V Leiden mutation	1.0 (0.6-1.7) [3] 2.0 (1.1-3.8) [4]	2.6 (1.0-7.0) [4]	1.4 (0.5-4.0) [4]		
Prothrombin 20210A mutation	1.3 (0.7-2.6) [38]	0.9 (0.3-3.3) [38]	-		
Homozygous defects or combinations of defects	0.8 (0.2-3.6) <sup>†</sup> [3] 2.9 (1.5-5.8) <sup>‡</sup> [4]	-	14.3 (2.4-86) <sup>†</sup> [3] 6.4 (1.0-39) <sup>‡</sup> [4]		
Mild hyperhomocysteinemia	0.8 (0.5-1.5)[39]	1.1 (0.2-6.2)[39]	-		
Elevated FVIII:c levels	1.2 (0.7-1.9)[39]	1.1 (0.4-3.1)[39]	-		
*Definition varies across studies. <sup>†</sup> combined thrombophilia defect vs. no defect. <sup>‡</sup> homozygous factor V Leiden vs. normal genotype.					
I.B. Case-control studies					
Thrombophilia defect	Sporadic miscarriage OR (95% BI)	Recurrent miscarriage* OR (95% BI)	Intrauterine fetal death* OR (95% BI)	Pre-eclampsia	
Lupus anticoagulant	3.0 (1.0-8.6) [6]	7.8 (2.3-26.5) [40]	2.4 (0.8-7.0) [6]	1.5 (0.8-2.8) [6]	
Anticardiolipin antibodies	3.4 (1.3-8.7) [6]	5.1 (1.8-14.0) [6] 3.6 (2.3-5.7) [40]	3.3 (1.6-6.7) [6]	2.7 (1.7-4.5) [6]	
Antithrombin deficiency	1.5 (1.0-2.5) [5]	0.9 (0.2-4.5) [5]	7.6 (0.3-196) [6]	3.9 (0.2-97.2) [6]	
Protein C deficiency	1.4 (1.0-2.1) [5]	1.6 (0.2-10.5) [5]	3.1 (0.2-38.5) [6]	5.2 (0.3-102.2) [6]	
Protein S deficiency	Heterogeneous data [5]	14.7 (1.0-218.0)[5]	7.4 (1.3-42.8) [5] 20.1 (3.7-109.2) [6]	2.8 (0.8-10.6) [6]	
Factor V Leiden mutation	1.7 (1.2-2.5) [5] 1.7 (1.1-2.6) [6]	2.0 (1.1-3.6) [5] 1.9 (1.0-3.6) [6]	3.3 (1.8-5.8) [5] 2.1 (1.1-3.9) [6]	2.2 (1.5-3.3) [6]	
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Homozygous defects or combinations of defects					
Mild hyperhomocysteinemia	6.3 (1.4-28.4) [6]	2.7 (1.4-5.2) [75] 4.2 (1.3-13.9) [6]	1.0 (0.2-5.6) [6]	3.5 (1.2-10.1) [6]	

## Risk of pregnancy complications in women with inherited thrombophilias.

Bates ASH education 2007

Thrombophilia	Early (recurrent) loss, OR (95% CI)	Late loss, OR (95% CI)	Pre-eclampsia, OR (95% CI)	Placental abruption, OR (95% CI)	IUGR, OR (95% CI)
Factor V Leiden (homozygous)	2.71 (1.32–5.58)	1.98 (0.40–9.69)	1.87 (0.44–7.88)	8.43 (0.41–171.20)	4.64 (0.19–115.68)
Factor V Leiden (heterozygous)	1.68 (1.09–2.58)	2.06 (1.10–3.86)	2.19 (1.46–3.27)	4.70 (1.13–19.59)	2.68 (0.59–12.13)
Prothrombin gene variant (heterozygous)	2.49 (1.24–5.00)	2.66 (1.28–5.53)	2.54 (1.52–4.23)	7.71 (3.01–19.76)	2.92 (0.62–13.70)
MTHFR C677T (homozygous)	1.40 (0.77–2.55)	1.31 (0.89–1.91)	1.37 (1.07–1.76)	1.47 (0.40–5.35)	1.24 (0.84–1.82)
Antithrombin deficiency	0.88 (0.17–4.48)	7.63 (0.30–196.36)	3.89 (0.16–97.19)	1.08 (0.06–18.12)	NA
Protein C deficiency	2.29 (0.20–26.43)	3.05 (0.24–38.51)	5.15 (0.26–102.22)	5.93 (0.23–151.58)	NA
Protein S deficiency	3.55 (0.35–35.72)	20.09 (3.70–109.15)	2.83 (0.76–10.57)	2.11 (0.47–9.34)	NA

# Secondary prophylaxis in RPL

- Brenner B, treated 50 women with RPL with clexane 40mg/d if single defect, 80mg/d if multiple, plus Aspirin if APA (commencing at confirmation of pregnancy till 6 weeks postpartum)
- Live births increased from 20% to 75% ( $p < 0.00001$ )
- One bleeding event (subchorionic haematoma) (Thromb Haem 2000)
- LIVE-ENOX study failed to show a benefit of higher dosing (Brenner JTH 2005)
- Gris et al, (Blood 2004) also showed a higher live birth rate 86% with 40mg enoxaparin cf aspirin in patients with 1 RPL > 10/40
- benefit of treatment in other complications of pregnancy is more controversial and individual

# Ovarian vein thrombosis

- OVT in pregnancy is rare (1 in 1000 deliveries) and typically postpartum
- Diagnosis is difficult as presents as fever and abdominal pain
- U/S sensitivity of 50%, CT is preferred
- Antibiotics and anticoagulation
- Risk in future pregnancy unknown but antenatal prophylaxis may not be needed

# Ovarian hyperstimulation syndrome

- Risk factor for venous thrombosis (up to 25%)
- Increased rate of upper limb DVT
- Prophylactic clexane

# Cardiac valves

- Concerns re valve thrombosis on LMWH
- “warfarin recommended”
- Stop warfarin 5 weeks; LMWH BD; then either:
  1. Switch to warfarin 13 weeks (?ICH risk)
  2. Remain on clexane
- Aspirin ?
- High risk: double star Edwards, mitral, AF, CVA

# Case 1

- 30yro lady
  - Returns from honeymoon OS pregnant and distal DVT
1. Continue anticoagulation full dose throughout entire pregnancy
  2. Reduce to prophylactic dose after 3mths
  3. Recommence prophylaxis postpartum ?

# Case 2

- 28yro 8 weeks pregnant
  - Had IVF
  - Extensive upper extremity DVT
  - Full dose LMWH
1. Mode of delivery
  2. Anticoagulation plan
  3. contraception

## Case 3

- 25yro with FVL, OCP and DVT
  - 8 weeks pregnant
1. Commence prophylactic LMWH
  2. Postpartum prophylaxis only
  3. If antenatal treatment anticoagulation plan at term

# Case 4

- 22yro first pregnancy IUGR
  - FVL homozygous – no personal VTE
  - Mother also homozygous FVL – no VTE, no other FHx
  - Pregnant 12 weeks
1. Postpartum prophylactic LMWH
  2. Antenatal prophylactic LMWH
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- 38yro with recurrent (3) 1<sup>st</sup> trimester fetal loss
  - FVL
1. Should have antenatal LMWH
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- 35yro recurrent DVT and APA on longterm warfarin
  - Became pregnant changed to clexane 100mg/d and aspirin
  - 20/40 developed fever and abnormal LFT with thrombocytopenia, normal coags and no fragments, changed to BD clexane and steroids
  - Worsening clinical condition with CT evidence of hepatic and splenic infarcts
1. Plasmapheresis
  2. Elective TOP
  3. Should she ever have another pregnancy

# Summary

- Thrombophilia important in VTE and complications of pregnancy
- Limited guidelines and evidence
- treatment is individual and sometimes difficult