THROMBOPHILIAS & PREGNANCY

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Welcome to the world of COCKTAILS
INTRODUCTION

• ‘Thrombophilia’ : Egeberg in 1965 ¹

• Norwegian family : Antithrombin deficiency → venous thrombosis

• At present: Used to describe a lab abnormality that increases the tendency to venous thromboembolism (VTE) ²

INTRODUCTION

• Can be acquired or inherited

• Acquired: APLA syndrome → combo of VTE + obs complications + LAC / APLA

• Cancer, surgery, strict immobilization, pregnancy & post partum period, OCPs, HRT all lead to a transient prothrombotic state

Creasy & Resnik's MFM. Sixth Ed. 2009 CH 40 P. 825-854.
INHERITED THROMBOPHILIAS

- Factor V Leiden Mutation
- Anti-thrombin Deficiency
- Protein C Deficiency
- Protein S Deficiency
- Prothrombin Gene 20210a Mutation
- Hyperhomocysteinemia
- Other Thrombotic Mutations
- Multifactorial
FACTOR V LEIDEN MUTATION

• Most common of serious heritable thrombophilias: reported by Bertina et al (1994)
• Substitution of glutamine for arginine at position 506 : site of proteolysis & inactivation by APC + PS: makes Factor Va resistant to inactivation by physiological anticoagulant.
• FVL: leading cause of APCR (90% of APCR)
• Responsible for 40% of VTE in pregnant patients
FACTOR V LEIDEN MUTATION

• APC inactivates Factor Va by cleaving the protein at arginine 506 cleavage site.

• In FVL mutation: arg → glu at 506, makes Factor Va resistant to activation by APC, i.e. APCR.

• Screening: assessing APCR → genotyping for FVL.

FVL & PREGNANCY

• Thought to be associated with foetal (>9 wks loss) & not embryonic loss

• Early pregnancy associated with low oxygen environment

• After 9 weeks, uteroplacental thrombosis reduces oxygen & nutrient delivery to fetus & hence adverse pregnancy outcomes.
FVL & PREGNANCY

• Possible association b/w FVL & abruption

• No clear association with FGR & pre-eclampsia

• Homozygous & heterozygous

• Factor V Hongkong, Cambridge & Liverpool also described
ANTITHROMBIN (AT) DEFICIENCY

- Rarest but most thrombogenic
- Type I: ↓ antigen & activity
- Type II: normal antigen & ↓ activity
- Type III: normal antigen & no activity
- VTE risk 25-fold increase, increases further with personal/family history (40%)
AT DEFICIENCY & PREGNANCY

- Increased risk of stillbirth after 28 weeks pug
- Data limited because of rarity
PROTIEN C DEFICIENCY

- Three types just like AT deficiency
- Data limited by small size of population
- Risk of VTE in pregnancy 2-8%
- Strong link with pre-eclampsia & abruption, not with stillbirth
PROTIEN S DEFICIENCY

- Modest thrombogenecity
- PS def + strong family history: risk of VTE in pregnancy is 6.6%
- PS in two forms: active free PS + PS bound to complement C4b binding protein
- Type I: low levels of both free & total PS
- Type II: low levels of free PS because of enhanced binding
PS DEFICIENCY & PREGNANCY

- Recurrent & non recurrent foetal loss > 22 weeks POG

- Also associated with pre-eclampsia

- Association with abruption not proved

- Data limited to draw conclusions

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PROTHROMBIN GENE MUTATION

- Guanine → adenine at nucleotide 20210 position in 3’ – untranslated region of the gene
- Increased translation → increased circulating levels of prothrombin
- Associated with 17% of VTE in pregnancy
- Synergistic hypercoagulable effects with FVL
- Family history increases risk
PTM & PREGNANCY

• Strong association with RPL

• Association with pregnancy loss increases with increase in gestational age

• Strong link with abruptio

• No significant link with FGR & pre eclampsia
HYPERHOMOCYSTEINEMIA

• Can result from a number of mutations

• Homozygous mutation in gene for MTHFR causes 25% rise in fasting homocysteine levels

• Hyperhomocysteinemia is a risk factor for VTE, same is not clear for MTHFR mutation per se
HYPERHOMOCYSTEINEMIA & PREGNANCY

- Thought to be associated with RPL (<16 weeks)

- Also with pre-eclampsia, FGR, still birth & abruption

- Fasting homocysteine level of > 12 µ mol/l to be considered positive.
ACQUIRED THROMBOPHILIAS

• Secondary to reduced coagulation inhibitor levels or increased levels or function of coagulation factors

• 1975: Nilsson et al reported a young woman with circulating LAC who had 3 RPL at 31 -34 weeks POG

• Elisa in 1980s made extensive studies possible
ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

• *Primary APS:* APS with no other recognized autoimmune disorders

• *Secondary APS:* when APS occurs in the setting along with other autoimmune conditions such as systemic lupus erythematosus
APS: WHAT TO KNOW??????

- Who should be tested for antiphospholipid antibodies?
- What laboratory criteria are used for the diagnosis of APS?
- Should women with APS have antepartum surveillance?
- How should APS be managed during pregnancy and the postpartum period?
- What is appropriate long-term management of APS?
ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

- International consensus statement for revised classification criteria given for diagnosis of APS in 2006

- At least one clinical (confirmed thrombosis or pregnancy morbidity) & one lab criteria (LAC, ACLA or anti β-2 glycoprotein-1 antibody) have to be met

- Upto 50% APS pregnancies have pre-eclampsia & 33% have FGR
ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

- Classification of APS not to be made if < 12 weeks or > 5 years separates the positive APLA test & clinical manifestation

- APS associated with RPL, abruption, FGR & severe pre-eclampsia

- LAC has greater risk of VTE compared with isolated ACLA
PATHOPHYSIOLOGY

• Myriad of mechanisms proposed for APA mediated arterial and venous thrombosis

• Direct inhibition of the anticoagulant effects of anionic phospholipid-binding proteins such as β₂-glycoprotein-1 and annexin V

• Inhibition of thrombomodulin, APC, and AT induction of TF, and VWF expression in endothelial cells

• Augmentation of platelet activation

• Induction of complement activation
CLINICAL CRITERIA FOR APS

• **VASCULAR THROMBOSIS:**

One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ confirmed by objective, validated criteria (i.e. Unequivocal findings of appropriate imaging studies or histopathology).

CLINICAL CRITERIA FOR APS

• PREGNANCY MORBIDITY:

A. One or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

B. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia or (ii) recognized uteroplacental insufficiency, or

C. Three or more unexplained consecutive euploid spontaneous abortions before 10 weeks of gestation, with maternal anatomic or hormonal abnormalities and paternal and parental chromosomal causes excluded

LAB CRITERIA FOR APS

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 wk apart, detected according to the guidelines of the scientific subcommittee on lupus anticoagulants/phospholipid-dependent antibodies

2. Anticardiolipin Antibody (ACL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 wk apart, measured by a standardized Elisa

3. Anti-β₂-glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile), present on two or more occasions, at least 12 wk apart, measured by a standardized Elisa, according to recommended procedures

SCREENING

• Antiphospholipid antibodies are directed against proteins bound to negatively charged surfaces, usually anionic phospholipids.

• APAs can be detected by
  (1) By screening for antibodies that directly bind protein epitopes such as β₂-glycoprotein-1, prothrombin, annexin V, APC, PS, etc.
  (2) By indirectly assessing antibodies that react to proteins present in an anionic phospholipid matrix (e.g. cardiolipin, phosphatidylserine)
  (3) By assessing the downstream effects of these antibodies on prothrombin activation in a phospholipid milieu (i.e. lupus anticoagulants)
MANAGEMENT

• Prednisolone: no more
• Treatment with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) plus low-dose aspirin (LDA) at 50 to 80 mg/day
• LDA from the time conception is planned
• Heparin as soon as FCA is confirmed
• Switch over to UFH at 36 wk POG
• Post partum prophylaxis
• Role of IV IG ??

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RECOMMENDATIONS: Inherited Thrombophilias

• Postpartum warfarin, LMWH, and unfractionated heparin anticoagulation can be used in women who breastfeed

• Inherited thrombophilia testing in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation reduces recurrence
RECOMMENDATIONS:
Inherited Thrombophilias

• There is insufficient evidence to recommend screening or treatment for thrombophilias in women with previous IUGR or preeclampsia

• Because of the lack of association between MTHFR and negative pregnancy outcomes, screening with fasting homocysteine levels or MTHFR mutation analyses is not recommended
RECOMMENDATIONS: Acquired Thrombophilias

• Obstetric indications for ALA testing should be limited to a history of one fetal loss or three or more recurrent embryonic or fetal losses

• Testing for ALA should be performed in women with a prior unexplained VTE, a new VTE during pregnancy, or in those with a history of VTE but not tested previously

• In women with APS and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered
RECOMMENDATIONS: Acquired Thrombophilias

• For women with APS who have had a thrombotic event, prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum may be given.

• For women with APS who have not had a thrombotic event, both, clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be used.

• Women with APS should not use estrogen-containing contraceptives.
FUTURE???

Can be asked at :

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THANK YOU...