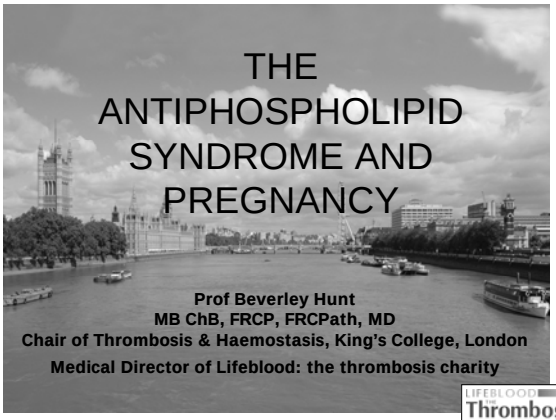

THE ANTIPHOSPHOLIPID SYNDROME AND PREGNANCY

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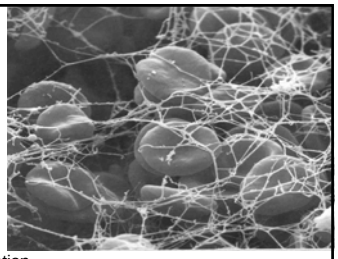
The antiphospholipid (Hughes) syndrome

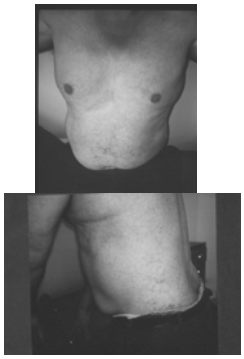
- Definition: A persisting antiphospholipid antibody associated with thrombosis &/or pregnancy morbidity
- PRIMARY isolated
- SECONDAY associated with another autoimmune disease, usually SLE, also myaesthenia gravis, rheumatoid arthritis
- It is a MULTISYSTEM disorder -skin, valves, thrombocytopenia etc

Characteristics of aPL –related thromboses



- 1) Thrombosis without inflammation
- 2) Affects ANY vascular bed
- Venous
- Microvascular
- Arterial
- Placental
- 3) Recurrent thromboses tend to occur in the SAME vascular bed
- 4) aPL promote atherosclerosis ?
- 5) Each patient has their own syndrome, not always full house.

APS is a multisystem disorder



10-20% have livedo reticularis

30% have cardiac valve abnormalites

Mild thrombocytopenia (plt >50 x 10^9/l) is a common feature

……and evidence of other auto-immune disease
- lupus
-12% have positive Coombs test
-thyroid disease
-coeliac disease etc

Detecting antiphospholipid antibodies

- Definition- 2 positive tests on two occasions more than twelve weeks apart
- Lupus anticoagulant (disastrous double misnomer)
- Anticardiolipin antibodies
- MUST DO BOTH!
- Can interfere with other functional thrombophilia assays -Protein C, Protein S.

CRITERIA FOR LUPUS ANTICOAGULANTS

Detect antibodies that inhibit in vitro phospholipid coagulation reactions

1. Prolongation of a phospholipid dependant clotting test.
2. There should be a relative correlation of the defect by the addition of phospholipids
3. Clotting time of a mixture of test and normal plasma should be longer than the clotting time of normal plasma (how true? Only 25% in our patients).

Laboratory lupus anticoagulant testing

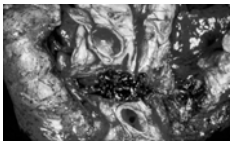
- APTT tests vary in their sensitivity to LA
  α concentration of phosphatidyl serine
- Guidelines BSH J Clin Path 1991; 44:885-9
  ISHT Thromb Haemost 1991; 65: 320-2
- NEQAS have shown 18% of labs failed to detect LA
  Jennings Brit J Haem 2002; 119: 364-69
- ? Need for reference & standardisation material

When to treat with anticoagulation?

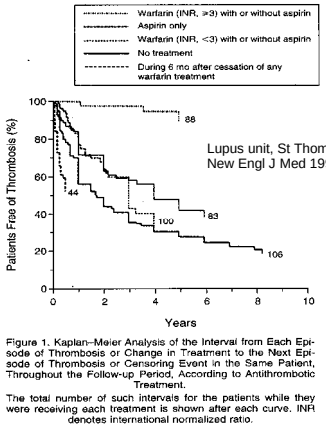
Clear aPL x 2 12 weeks apart

and

a thrombotic event



Post-mortem PE



Lupus unit, St Thomas.
New Engl J Med 1995; 332: 993-7

Figure 1. Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.
The total number of such intervals for the patients while they were receiving each treatment is shown after each curve. INR denotes international normalized ratio.

Healthy patients with antiphospholipid antibodies

- No evidence-base
- Offer regular review
- ? Aspirin 75mg daily if tolerated
- Thromboprophylaxis at time of haemostatic stress
- Contraception - POP, Depo-Provera, Mirena coil, no HRT

Pregnancy & antiphospholipid antibodies

Classification Criteria for definite antiphospholipid syndrome

Antiphospholipid antibody (aPL) plus

- One or more unexplained deaths of a morphologically normal fetus BEYOND the 10th week of gestation, OR
- One or more premature births of a morphologically normal neonate at or before 34th week of gestation because of PET, eclampsia or severe placental insufficiency
- OR
- THREE or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with other causes excluded

Antiphospholipid syndrome during pregnancy risks to fetus

<u>Ist trimester</u>
Risk of miscarriage
(inhibit trophoblast
Implantation)

APS*

Uteroplacental insufficiency

Placental dysfunction

I U DEATH

IUGR†

<u>2rd & 3rd trimester</u>
Pre-eclampsia
Intra-uterine growth restriction
Placental abruption

*APS = antiphospholipid syndrome; †IUGR = intra-uterine growth retardation

Antiphospholipid Syndrome: Placental pathology

"Extensive infarction and thrombosis together with other non-specific features accredited to hypoxia"

De Wolf et al, 1982

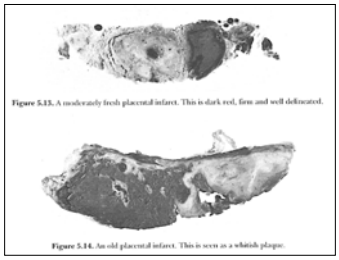
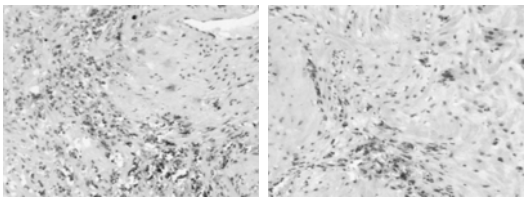


Figure 5.13. A moderately fresh placental infarct. This is dark red, firm and well delineated.

Figure 5.14. An old placental infarct. This is seen as a whitish plaque.

But also an inflammatory component: High concentration of macrophages in APS placental bed biopsy



APS biopsy Control biopsy

Stone et al, Placenta 2006; 27: 457

Antiphospholipid Syndrome: Placenta - pathological mechanisms

"Reduction of annexin V on placental villi of women with antiphospholipid antibodies and recurrent spontaneous abortion" *Rand et al, AJOG 1994*

"Fetal stem vessel endothelial changes in placentae from normal and abnormal pregnancies"
Labarrere & Faulk, Am J Repr Immunol 1992

aPL risks in pregnancy

MOTHER	FETUS
• Increased risk of thrombosis	• Inhibition of trophoblast invasion-1st trimester loss
• Pre-eclampsia (10%)	• Placental dysfunction- growth restriction & death, pre-eclampsia, abruption
• Iatrogenic damage	• Iatrogenic damage
• (SLE flare)	(Anti-Ro: neonatal lupus & complete heart block)

Antiphospholipid Syndrome in pregnancy – treatment principles

aspirin+/-heparin

&

close obstetric surveillance by a multidisciplinary team

&

early intervention

Management of aPL in pregnancy

Joint clinics-haematology, obstetric & rheumatology

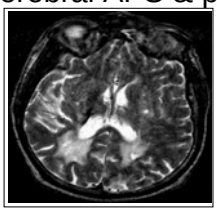
MOTHER	FETUS
• PRECONCEPTUAL CONSELING (timing, risks, plan) • Appropriate thromboprophylaxis in pregnancy and post--partum	• Placental protection • Intrauterine artery Dopplers at 24 weeks • Regular fetal monitoring from 20 weeks • Mode/timing of delivery

Using LMW heparin in aPL

in the Lupus pregnancy unit, GSTT

Thromboprophylaxis	Placental protection
• Previous venous aspirin 75mg plus enoxaparin 40mg s.c OD then BD at 16-20 weeks • Previous arterial Aspirin 75mg plus enoxaparin 40mg BD throughout	• different

Previous cerebral APS & pregnancy



- 5% recurrent events (despite full-dose LMW & UF heparin), but did well on warfarin.
- Hunt et al. Thromb Haemost 1998; 79:1060.
- If any neurological events, increase LMWH, switch to warfarin if events continue.
- Run INR at 2-2.5. Check twice weekly
- Switch back to UFH 2 weeks prior to delivery

Management of APS when previous pregnancy morbidity

First trimester

- Previous thrombosis- this management dominates

Otherwise

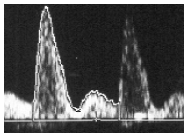
- Aspirin 75mgs or aspirin + LMWH
- When to stop LMWH?

Second and third

- Includes PET, IUGR, IUD, abruption
- Previous thrombosis- this management dominates
- Aspirin 75mg + Clexane 40mg s.c. OD until 6/52 post partum

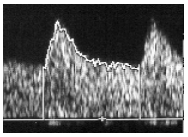
Uterine artery Doppler analysis at 20-24 weeks is predictive of outcome

Flow velocity waveforms



Abnormal FVW:

high RI, early diastolic notch



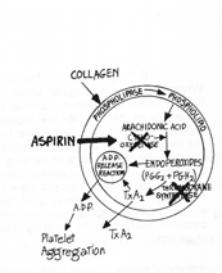
Normal FVW:

low RI, no notch

If previous recurrent first trimester loss and Normal Dopplers at 20 weeks, we stop LMWH

Best predictor of fetal outcome is past obstetric history
Primigravida with aPL & no previous thrombosis?

- Intensive maternal & fetal monitoring
- Aspirin 75mgs
- Post partum thromboprophylaxis



Obstetric analgesia and Clexane

- <u>Thromboprophylaxis</u>
- Can have regional anaesthesia if last LMWH dose > 12 hours previously & normal clotting screen and platelets >70 x 10^9/l

<u>Treatment doses</u>

No regional anaesthesia unless > 24 hours since last dose & normal clotting screen and platelets >70 x 10^9/l

Post-partum

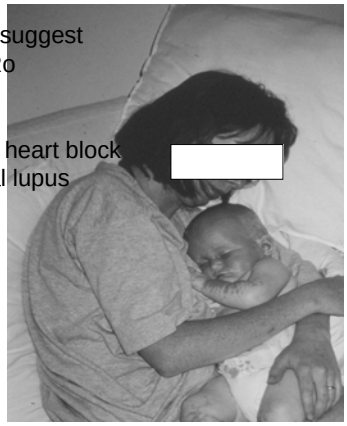
- 6 weeks thromboprophylaxis for those not on warfarin
- Switch back to warfarin at patient's convenience unless cerebral APS- switch back ASAP

Thrombocytopenia in APS pregnancies

- Many patients have a mild autoimmune thrombocytopenis outside of pregnancy (80-150 x 10^9/l
- Rarely severe in pregnancy
- If also on thromboprophylaxis, aim to keep platelet count greater than 50 x 10^9/l with prednisolone (rarely need more than 20mg)

If aPL positive then suggest Screening for anti-Ro

Anti-Ro
2% risk of complete heart block
10% risk of neonatal lupus



Review of 83 APS pregnancies (in press)

- Group 1 previous 1st trimester recurrent miscarriage (21)
- Group 2 IUD or early delivery due to PET or FGR (21)
- Group 3 Previous thromboembolism (41)
- Group 2 had significantly longer gestation (38 wk (28-41) than previously 24 (18-35) $p<0.0001$) and 100% live birth rate
- Rate of FGR was high in Group 1 (27%)

Conclusions

- Diagnosis of APS is difficult
- Once APS is diagnosed, the use of aspirin and LMWH improves outcome