Antiphospholipid syndrome

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Introduction

- APS was first described in 1980s by Graham Hughes
  - Recurrent thrombosis and miscarriage

- Complex entity with high morbidity for both mother and fetus.

Definition

- A persisting antiphospholipid antibody associated with thrombosis and/or pregnancy morbidity.

- Types
  - **Primary**: isolated.
  - **Secondary**: associated with another autoimmune disease, usually SLE, also myasthenia gravis, rheumatoid arthritis.

Incidence

- 1 - 5% of the general obstetric population have aPL
  - Minority of these individuals develop APS
- About 12 – 30% of women with SLE have aPL
- About 30% of those with aPL have thrombosis
- Up to 30% of women with severe early onset PET may have aPL

Clinical presentation

- **Obstetric APS**
  - Recurrent 1st trimester miscarriages
  - Ischaemic placental insufficiency
    - PET, Eclampsia, stillbirth and IUGR
- **Thrombotic manifestations**
  - Recurrent unprovoked DVT
  - PE
  - Thrombosis in the arterial system or unusual venous sites

The Lancet 2010

- Other manifestations of APS
  - Cerebral involvement
    - ✓ Epilepsy
    - ✓ Cerebral infarction
    - ✓ Chorea and migraine
    - ✓ Transverse myelitis

Diagnosis

- Two clinical scenarios that should raise clinical suspicion for APS
  - ✓ Unexplained venous or arterial thrombotic events in young patients
  - ✓ Adverse pregnancy outcome:
    - includes fetal death after 10 weeks,
    - premature birth due to severe preeclampsia or placental insufficiency or
    - multiple embryonic losses (< 10 weeks gestation)

APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical criteria

1. Vascular thrombosis

One or more clinical episodes or arterial, venous or small vessel thrombosis, in any tissue or organ.
Thrombosis must be confirmed by objective validated criteria (e.g., imaging or Doppler studies or histopathology)

2. Pregnancy morbidity

a. **One or more unexplained deaths** of a morphologically normal fetus **at or beyond the 10th week** 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:
eclampsia or severe preeclampsia defined according to standard definitions, or
recognized **features of placental insufficiency** (e.g., abnormal Doppler flow, abnormal fetal testing, SGA <10%, oligohydramnios) or

c. **Three or more unexplained consecutive spontaneous abortions before 10th week** of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

The presence of aPL on ≥2 occasions at least 12 weeks apart

a. Presence of **lupus anticoagulant** in plasma or serum

b. **Anticardiolipin antibody of IgG and/or IgM** isotype in serum or plasma, present as **>40 GPL or MPL** or > 99th percentile

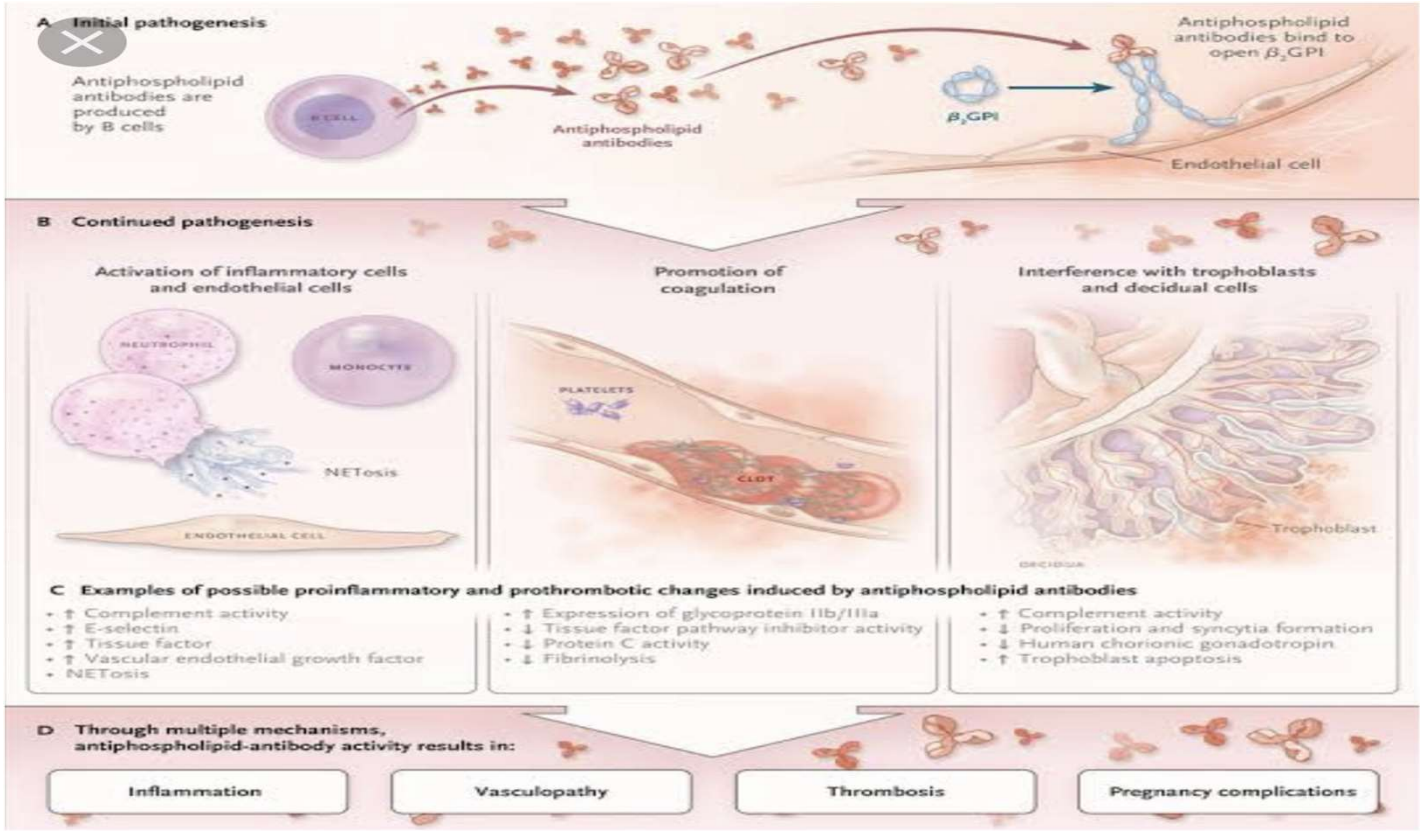
c. **Anti-B2 glycoprotein-I of IgG and/or IgM** in plasma or serum (in titer >99th percentile for normal population)

The Sydney Criteria for APS Miyakis J Thromb Haem 2006

Pathogenesis

- The pathogenesis of aPL related pregnancy morbidity is incompletely understood.
- Genetic predisposition seems to contribute and environmental factors especially smoking.
- All individuals with aPL do not develop clinical symptoms.
- The mere presence of aPL is not sufficient to cause APS manifestations.

Pathogenesis



Who to screen?

- History of thrombosis
- Recurrent miscarriages
- IUD
- Severe early onset PET
- FGR

Antiphospholipid antibodies – what are they?

Lupus anticoagulant (LA)
Anticardiolipin antibodies (ACA)
Anti-B2 GPI

Heterogeneous antibodies against phospholipid binding proteins
Common in healthy population – prevalence of LA 1 - 3.6% & ACA 1- 5.6%
Stronger association of LA with thrombosis than ACA and the role of B2GPI still under debate

Which aPL are pathogenic?

- **Lupus anticoagulant** – strongest predictor of thrombosis
  - ✓40X increase stroke risk
  - ✓5X increase MI risk in women <50
  - ✓Strong association with recurrent miscarriage <24 weeks

- **Anticardiolipin**
  - ✓Persistent ACA & LA – more thrombosis
  - ✓Both IgM and IgG ACA associated with miscarriage risk

- **B2GPI antibodies**
  - ✓Not associated with thrombosis, miscarriages in 3 reviews

Ruiz-Irastorza et al The Lancet 2010

Which aPL are pathogenic?

- ACA, B2GPI and LA: triple positivity
    - Associated with the highest risk for thrombotic manifestations in APS

Complications in pregnancy

- Maternal
  1. Venous and arterial thrombosis
     - ✓ Risk is 5 – 12%
  2. Preeclampsia
     - ✓ Incidence of PET is increased from 18 – 48%
     - ✓ Significant association between PET and ACA
  3. Autoimmune thrombocytopaenia
     - ✓ Risk is 40 – 50%
  4. Other medical complications
  5. Catastrophic APS
     - ✓ Rare, progressive thrombosis, multiorgan failure and death may occur.

Complications in pregnancy

- Fetal
  1. Pregnancy loss and fetal death
     - ✓ May occur in any trimester and can be recurrent
     - ✓ About 5 – 20% of women with RPL have aPL
  2. FGR
     - ✓ Occur in 15 - 30% of cases
  3. Preterm birth
     - ✓ About 33%, secondary to HPT or placental insufficiency
  4. Placental abruption

Management of APS

- The goal of treatment is to reduce maternal morbidity and improve fetal outcome.

- Management should start with prepregnancy counselling, focusing on involved risks.

- Multidisciplinary management
  - ✓Rheumatologist
  - ✓Internal medicine

Management of APS

- Antenatal
  - Close fetal monitoring.
  - Uterine artery Doppler's at 20 – 24 weeks.
  - Monthly growth scans at 28 weeks if uterine artery Doppler's are abnormal.
  - Regular BP checks and urinalysis
  - Screening for anti-Ro
    - ✓2% risk of complete heart block
    - ✓10% risk of neonatal lupus

Management of APS

- No thrombosis, no miscarriage, no adverse pregnancy outcome
    - Aspirin 75mg daily from preconception

Management of APS

- Previous thrombosis
  - ***On maintenance warfarin***: transfer to aspirin and LMWH bd as soon as pregnancy confirmed.
  - ***Not on warfarin***: aspirin 75mg daily from preconception and commence LMWH daily once pregnancy confirmed. Increase LMWH to bd at 16 – 20 weeks

Management of APS

- Recurrent miscarriages <10 weeks
  - No therapy
  - ***No prior anticoagulant therapy***: aspirin 75mg daily from preconception
    - LB rate in women treated with aspirin alone is 70 – 80%
  - ***Prior miscarriage with aspirin alone***: aspirin 75mg daily from preconception and LMWH daily once pregnancy confirmed. Consider discontinuation of LMWH at 12 or 20 weeks if uterine artery waveform is normal.

Prevention of recurrent miscarriages for aPL+

- Metaanalysis of 13 studies (n=849)
  - **UFH plus ASA** (n=140, 2 trials) reduced pregnancy loss compared to ASA alone (RR 0.46, 95% CI 0.29 – 0.71)
  - **LMWH plus ASA** (n=98, 1 trial) equivalent to ASA (RR 0.78, 95% CI 0.39 – 1.57)
  - **ASA alone** (n=286, 3 trials) did not significantly reduce pregnancy loss (RR 1.05, 95% CI 0.66 – 1.68)
  - ACCP 2012 Guidelines: recommend UFH or prophylactic LMWH plus LDA in those confirmed aPL and >3 early pregnancy loss over no treatment

Cochrane Database Empson et al 2008

Management of APS

- Late fetal loss, neonatal death, or adverse outcome due to preeclampsia, FGR or abruption
  - Aspirin 75mg daily from preconception and LMWH daily once pregnancy confirmed.
  - 3 meta-analysis of RCT: combination of ASA and heparin significantly reduced pregnancy loss (RR 0.46) or first trimester loss (OR 0.39) and increased live births

Obstet Gynecol 2010
Rheumatol 2009

Other therapies

- Corticosteroids and intravenous immunoglobulins

- Metaanalysis showed no reduction in pregnancy loss in women treated with LDA and prednisone

- IVIG:
  - ✓Expensive
  - ✓No benefit relative to heparin & LDA
  - ✓Reserved for cases refractory to ASA and heparin

Other therapies

- Corticosteroids
  - ✓Abandoned
  - ✓Do not improve the live birth
  - ✓Significant maternal & fetal morbidity

Laskin et al 1997

Treatment of catastrophic APS

- Proposed diagnostic criteria

1. Involvement of 3 or more organs, systems, tissues
2. Simultaneous onset symptoms or within 1 week
3. Small vessel occlusion (histologically confirmed)
4. Positive aPL

Treatment of catastrophic APS

- Aggressive approach
- Combined treatment that includes anticoagulation with heparin, high dose steroids, plasma exchange and/or intravenous immunoglobulins.
- Refractory catastrophic APS
  - Cyclophosphamide
  - Prostacyclin
  - Fibrinolytic agents

Postpartum

- Women on long-term warfarin →recommence treatment
- Women with previous thrombosis → LMWH for 6 weeks
- Women without previous thrombosis → LMWH for at least 10 days to 6 weeks, depending on risk factors
- Estrogen containing oral contraceptives are contraindicated

Conclusion

- Pregnant women with APS are at risk of complications at all stages of pregnancy.

- Prospective studies are needed to determine which treatments are best suited for women with different risk profiles.

- Thanks