Obstetric antiphospholipid syndrome

Johannes Vermeer: Women holding a balance
The National Gallery of Art, NW, USA

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Women with APS are at increased risk for:
miscarriage,

preeclampsia,

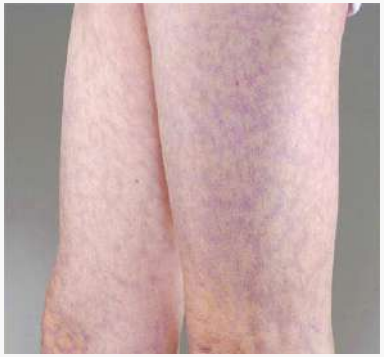
fetal or neonatal death,

intrauterine growth restriction and

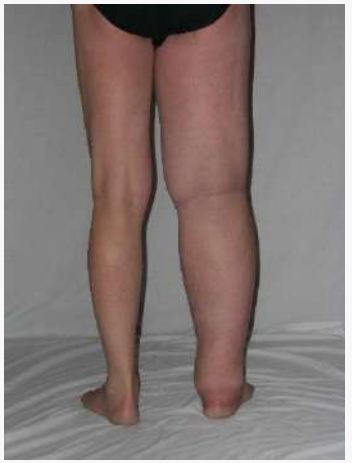
thrombotic complications during pregnancy

Identifying women destined for these complications remaines challenging and limits our ability to counsel and care for them

Johannes Vermeer: Women holding a balance,
The National Gallery of Art, NW, USA



Who is an OAPS patient?



The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 247 consecutive cases

- 338 women, 1253 pregnancies
- 247 Sydney criteria
- **192 (77.7%) live births**
- 55 (23.3%) with misscariages: 38 (69%) treated with LMWH and LDA
- 177 from 247 women (72%) were treated with LMWH and LDA

- recurrent miscarriages (≥ 3, week <10): triple +
- fetal loss (≥ 1, week >10): triple +
- early preeclampsia: LAC +
- intrauterine growth restriction: LAC + och triple +
- prematurity: LAC +

Alijotas-Reig J et al. Autoimmun Rev 2015;14:387-95

PROMISSE study

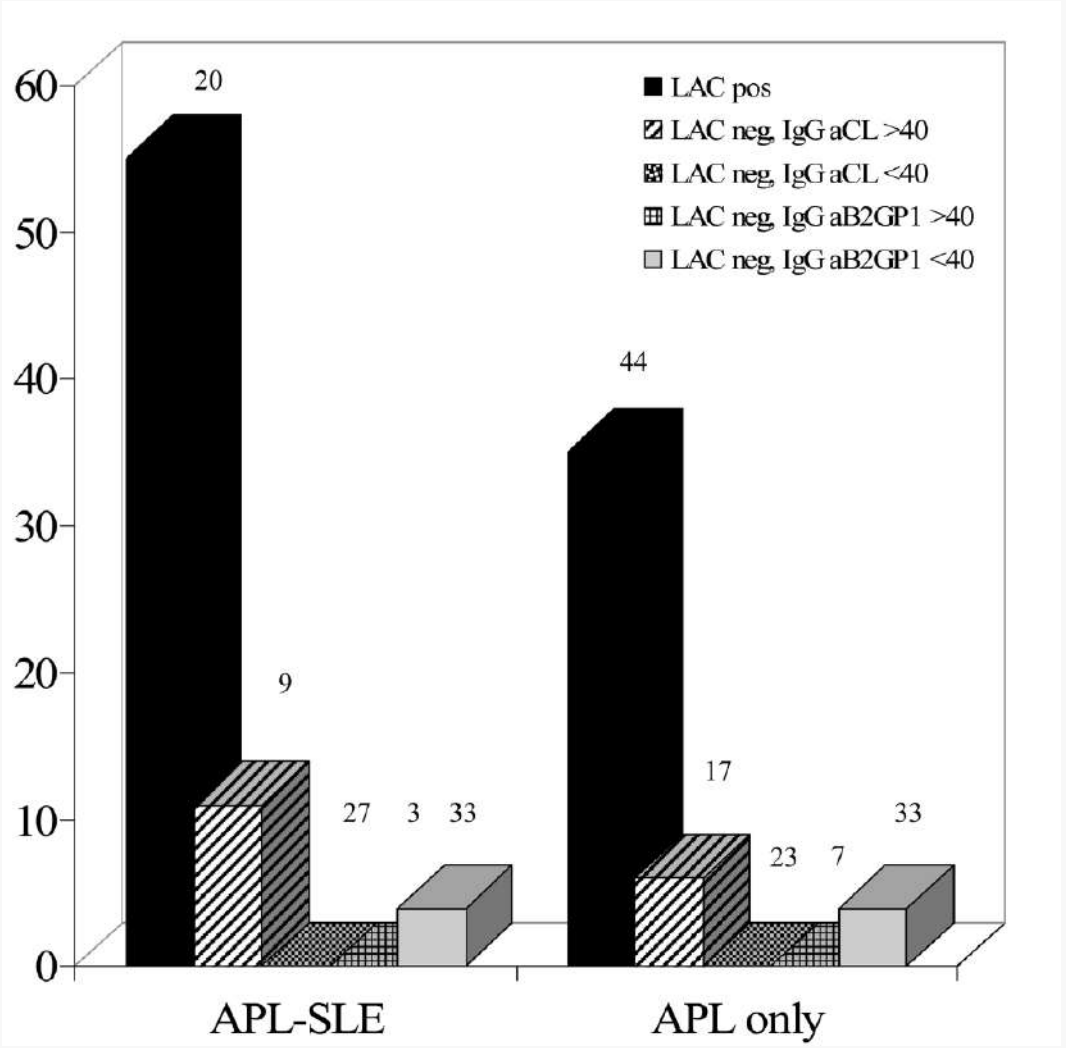
SLE + aPL or aPL+ pregnancies

prospective follow-up each month

Factors associated with complications:

LAC or aCL >40E (p<0.0001)

SLEDAI >4 (p=0.02)



Lockshin M. et al. Arthritis Rheum . 2012 ; 64: 2311–2318

Obstetric outcomes in patients with primary TAPS and OAPS and its relation to the aPL profile.

- retrospective single-centre study
- 30 pregnant women with PAPS (2000-2016)
- control group: all pregnancies in Stockholm county during the same period

- preeclampsia ($p < 0.001$),
- low birth weight at delivery ($p = 0.001$),
- Apgar < 7 at 5 minutes ($p < 0.001$) and
- small infants ($p < 0.001$) were more common in APS compared to controls.

- **Previous OAPS patients** had a higher incidence of adverse pregnancy outcomes than patients with TAPS, especially **triple positive.**

Högden A. et al. Lupus 2019;28:868-877

The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 1000 consecutive cases.

- 1000 women, 3553 events
- all fulfilled Sydney criteria

- miscarriages: 386 (38.6%)
- early preeclampsia: 181 (18.1%)
- intrauterine growth restriction: 161 (16.1%)

live-birth rate:

- patients with recommended treatment 85%
- patients with no treatment 49.6%

"OAPS is the most frequently treatable autoimmune disorder during pregnancy"

Alijotas-Reig J et al. Autoimmun Rev 2019;18:406-14

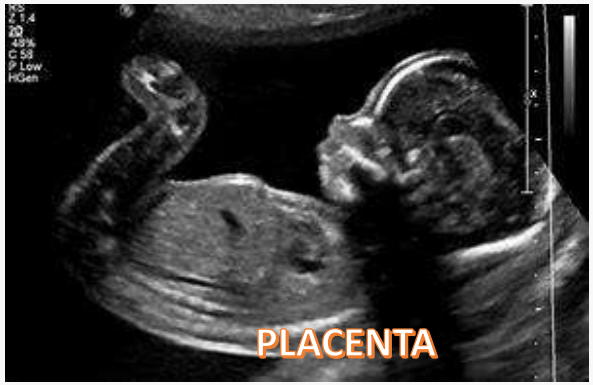
Mechanisms of placental damage in APS

Preventing poor pregnancy outcomes requires an understanding of mechanisms of injury

Thrombosis

Impaired Annexin5 shield

- ⬆ TF expression
- ⬆ cellular activation
- ⬇ PC activity



Abnormal placentation

Abnormal endometrial diferentiation

- ⬇ angiogenesis
- ⬇ Trophoblast
- ⬆ trophoblast apoptosis

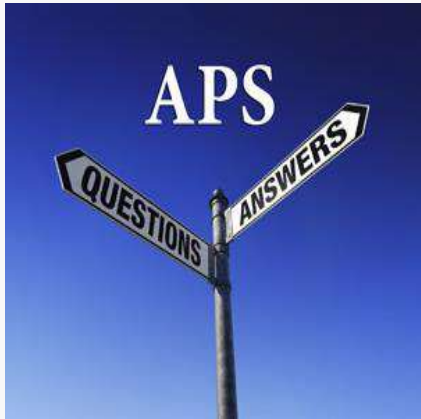
Abnormal spiral artery transformation

Inflammation:

Comlement activation

Inflammatory infiltrates

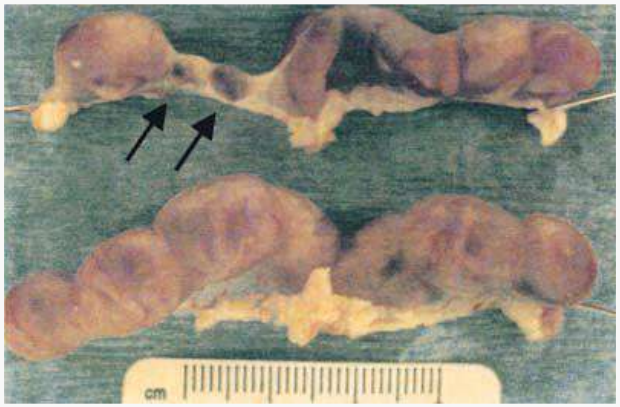
Cytokine dysregulation



Experimental models of OAPS

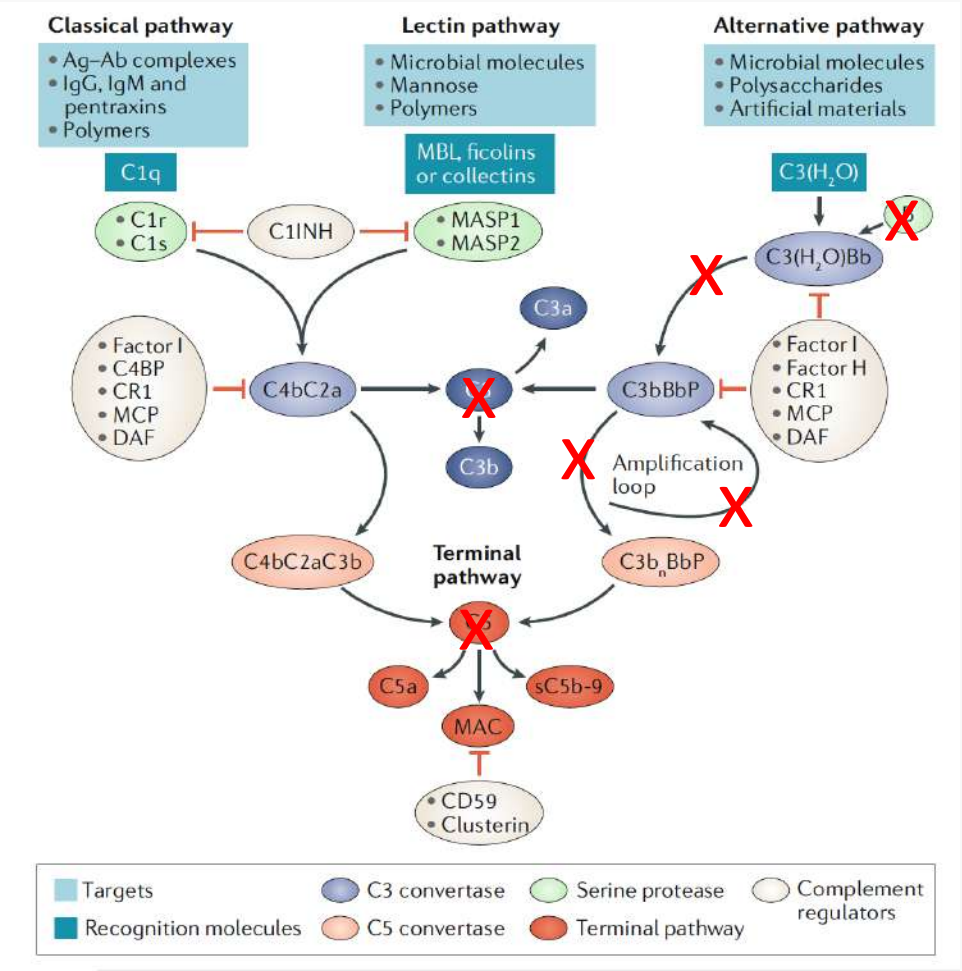
aPL IgG

control IgG



Holers et al. J Exp med 2002; 2:211-20

Complement activation: Experimental Models of OAPS

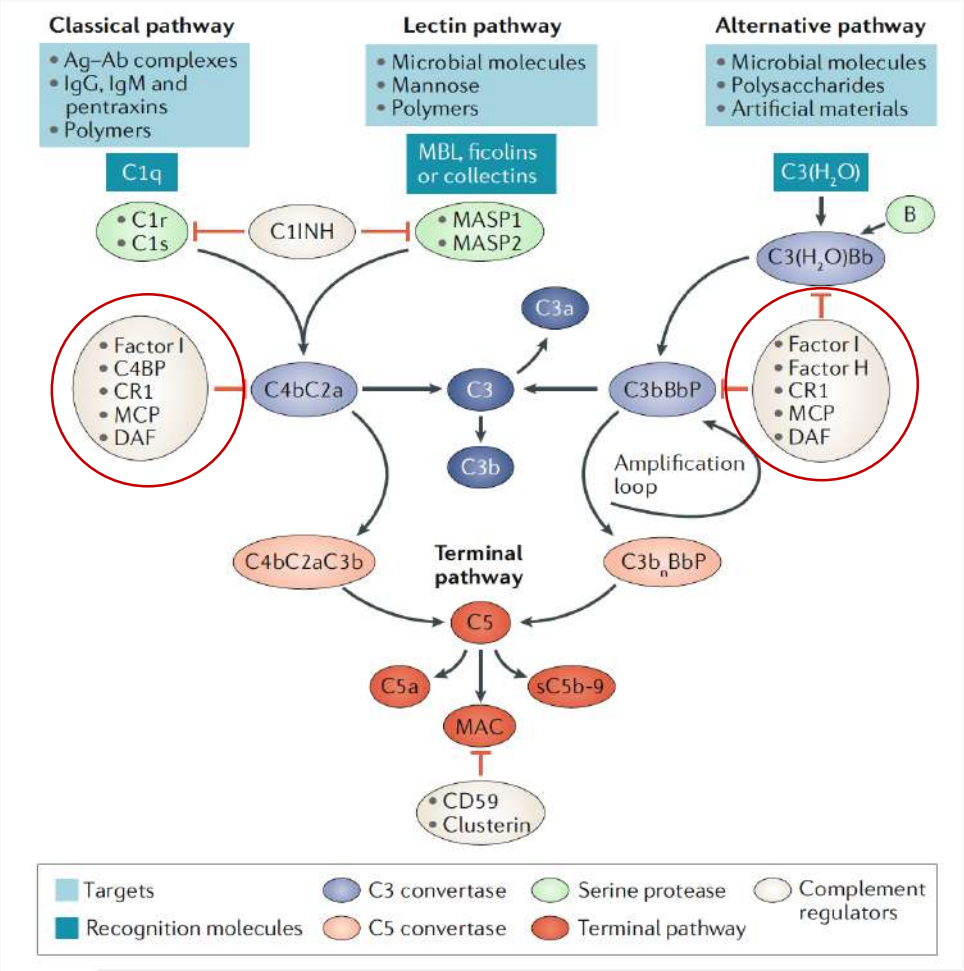


Murine models of pregnancy complications induced by aPL antibodies implicate **complement activation** as an essential and causative factor in fetal loss and growth restriction.

Blockade of the alternative pathway (factor B), C3, C5 or C5aR rescues the fetal death and prevents growth restriction in aPL treated pregnanat mice.

Girardi G. et al. J Clin Invest 2003; 112:1644-54
Girardi G. et al. Nat Med 2004; 10:1222-6

Complement activation: Evidence in human pregnanacy complications

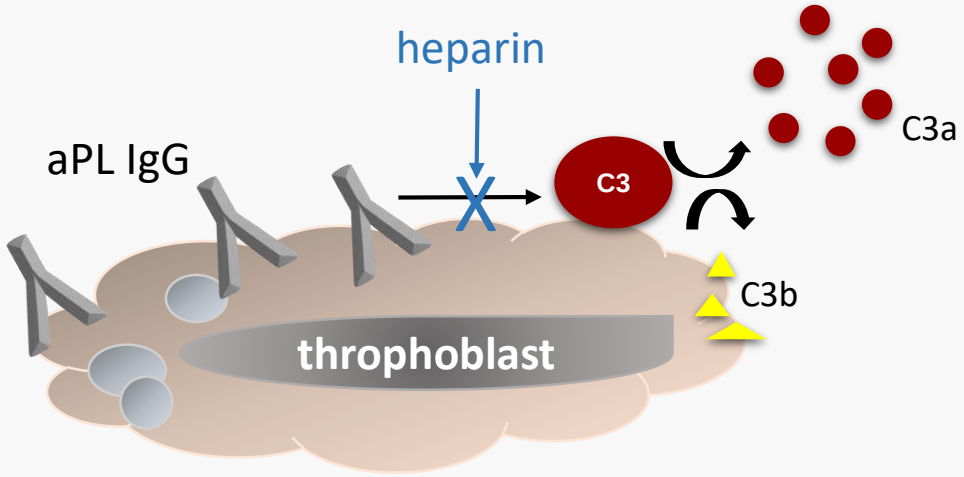


C4d (classical pathway) is present in the fetal-maternal interface in placentas from women with SLE and/or APS and from women with preeclampsia

Mutations of complement regulatory proteins predispose to preeclampsia in patients with SLE and/or APS

- Schamonki JM et al. Am J Obstet Gynecol 2007; 196:167.e1-5
- Cohen D et al. J Pathol 2011; 225:502-11.
- Buurma A et al. Hypertension 2012; 60:1332-7
- Viall CA. Autoimmun Rev 2015; 14:446-71

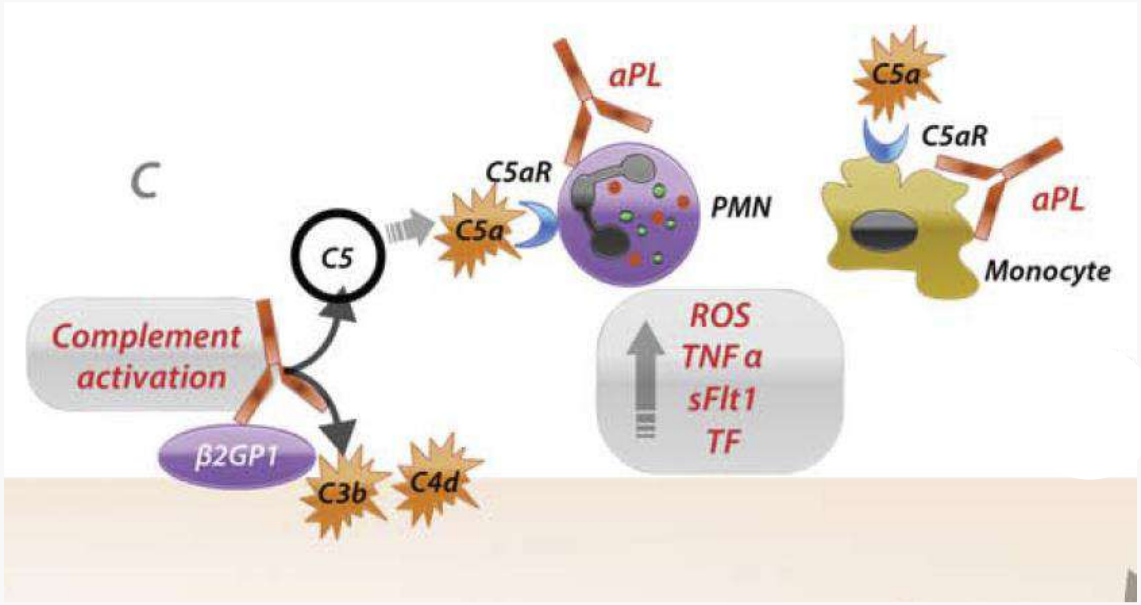
Heparin inhibits complement activation



The effectiveness of heparin in the prevention of obstetric complications in women with APS may be due to their inhibitory effects on C3 clevage rather than their anticoagulant effects

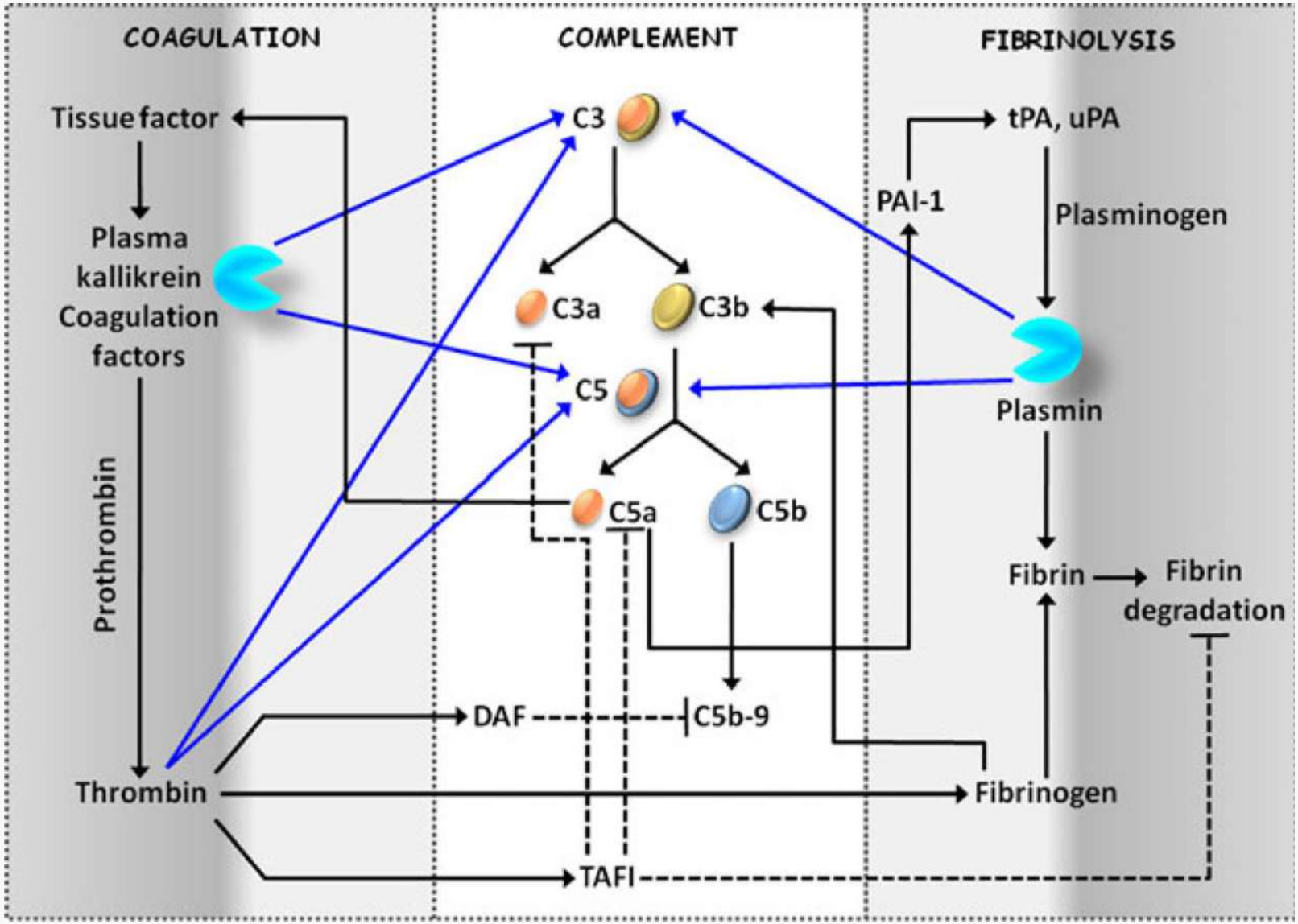
Girardi G et al. Nature Med 2004; 10: 1222-6.

TNFα in experimental models of OAPS

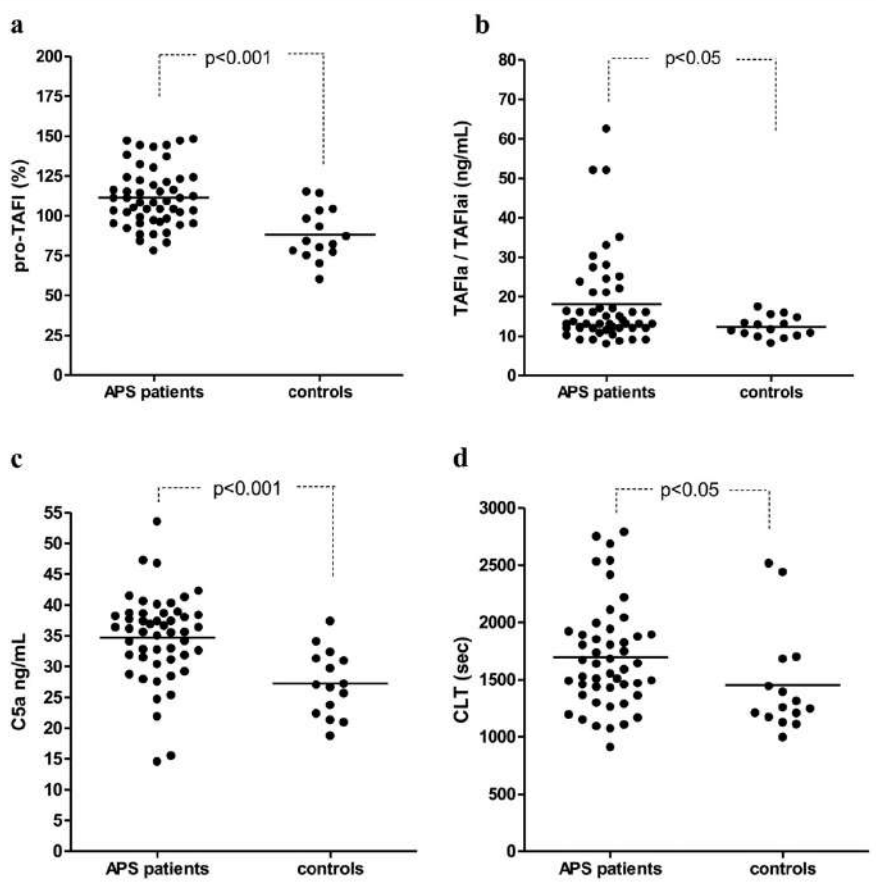


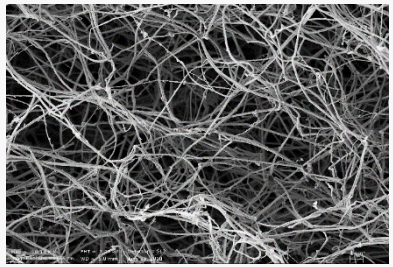
- In pregnant mice treated with aPL, TNF-α is an essential and caustive factor in fetal loss and growth restricition
- Treatment with aPL causes rapid increase in plasma TNF-α in preganant but not in non-pregnant mice and occurs downstream of complement activation
- TNF alfa deficient mice are protected from aPL induced fetal loss
- TNF alfa blockade attenuated aPL induced fetal loss

Berman G et al. J Immunol 2005; 174: 485-90.

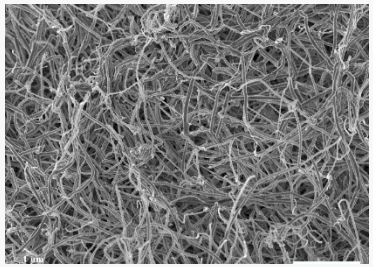

COAGULATION
COMPLEMENT
FIBRINOLYSIS
Tissue factor
Plasma kallikrein Coagulation factors
Prothrombin
Thrombin
C3
C3a
C3b
C5
C5a
C5b
DAF
C5b-9
TAFI
PAI-1
tPA, uPA
Plasminogen
Plasmin
Fibrin
Fibrin degradation
Fibrinogen

TAFI - A possible link between coagulation and complement activation in APS





Control

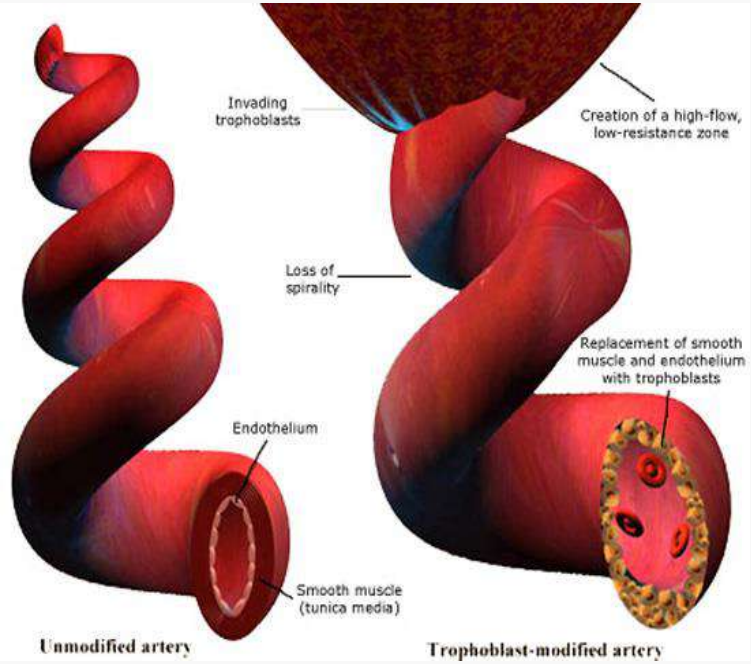


Patient with APS

Grosso G. et al. Thromb Res 2017; 158: 168-73.
Vikerfors A. et al. Thromb Res 2015; 133: 936-44.

Preeclampsia

A pregnanacy specific disorder defined by the appearance of hypertension and proteinuria usually after the 20th weeks of gestation

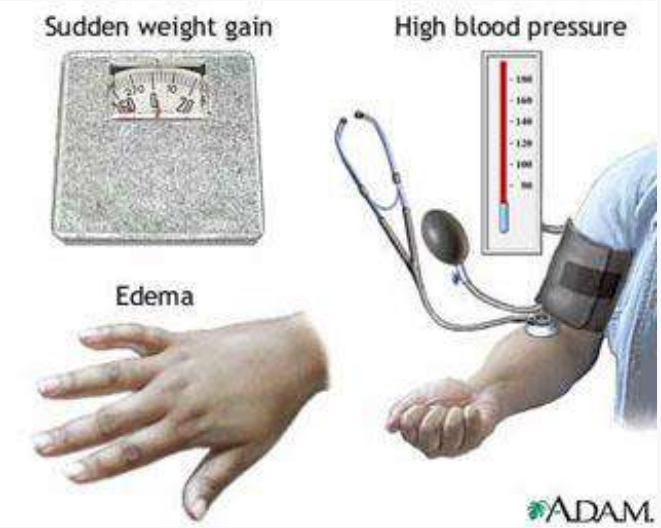


preeclampsia helathy

First stage: Failure of remodeling of uterine spiral arteries and due to that hypoperfusion of placental intervillous space. The 1st trimester is when it starts and is clinicaly scilent.

Second stage: Maternal endothelial dysfunction as a systemic response to placental hypoperfusion, mediated by placental secretion of anti-angiogenic factors.

Preeclampsia



Complement blokade and TNF-α blokade:

in murine model

- prevents placental dysfunction
- allows spiral artery remodeling
- Prevents angiogenic dysbalance
- Attenuates fetal loss
- Attenuates fetal growth restriction

Gelber S et al. J Immunol 2015; 195:1129-1138.

POMISSE-Complement activation

- In SLE and/or aPL positive patients elevated levls of Bb and to less extent sC5b-9 detectable early in pregnanacy (12-15 weeks) are independently associated with APO.
- The association is stroger in the presence of aPL antibodies

- A rational for testing downstream patways to prevent APO in high risk SLE/APS patients?

►► Women, 32 years old, previously healthy, without any treatment.

►► No family history of rheumatic desease, venous thromboembolims (VTE) or cardiovascular disease (CVD).
None-smoker. No other risk factors for VTE or CVD.

►► 3 children, normal pregnancies and deliveries

►► **2017:** recurrent arthritis of the knee joints, debut after the 3rd birth, 8 moths ago
RF- och anti-CCP negative. ANA negative, dsDNA-antibodies negative.
HLA-B27 positive

►► Diagnosis: **HLA-B27 positive oligoarthritis**
Treatment: Salazopyrine – leukopenia and skin rash.

►► TNF-alfa blockade: Cimzia® (certolizumab pegol) ⇨ in remission

►► **February 2019:** pregnant, week 8

Antenatal clinic: high risk pregnancy

- **ANA negative**
- **LAC positive:** dRVVT-ratio = 1.52; APTT-ratio = 1.58

  (ref. negative <1,2; positive >1.4)
- S-cardiolipin IgG, IgM, IgA negative.
- S-β_2-GPI IgG, IgM, IgA negative.

►► **Treatment? LDA? LMWH? Both?**

►► **LAC positive after 12 weeks**

►► Women, 32 years old, HLA-B27 positive oligoarthritis,
3 children, normal pregnancies and deliveries,
LAC positive during the 4th pregnancy

►► **Treatment:** LDA – Trombyl 75mg/day

- *In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg/day) during pregnancy should be considered.*
  - *Tektonidou MG, et al. Ann Rheum Dis 2019;0:1–9*

►► Week 34: DVT right a. femoralis

►► **Diagnosis: APS**

►► **Treatment:** Trombyl 75mg/day + LMWH, therapeutic dosage

KAROLINSKA
Universitetssjukhuset

Karolinska Institutet

Thank you for the attention

Women with APS are at increased risk for miscarriage, preeclampsia, fetal or neonatal death and intrauterine growth restriction.

Identifying women destined for these complications remaines challenging and limits our ability to counsel and care for them.

Treatment to prevent poor pregnancy outcomes require an understanding of mechanisms of injury.

Gustav Klimt, Hope II, 1907-8. Museum of modern art, New York