

Service d'Hématologie
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**FORMATION CONTINUE DU SERVICE
D'IMMUNOLOGIE ET ALLERGIE**
Autoimmunité
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Les problèmes de crase chez la patiente lupique enceinte

- The antiphospholipid antibodies and their antigenic targets
- The pathogenesis of the antiphospholipid syndrome
- Clinical presentation
- Diagnostic methods
- Treatment

An autoimmune disease associating:

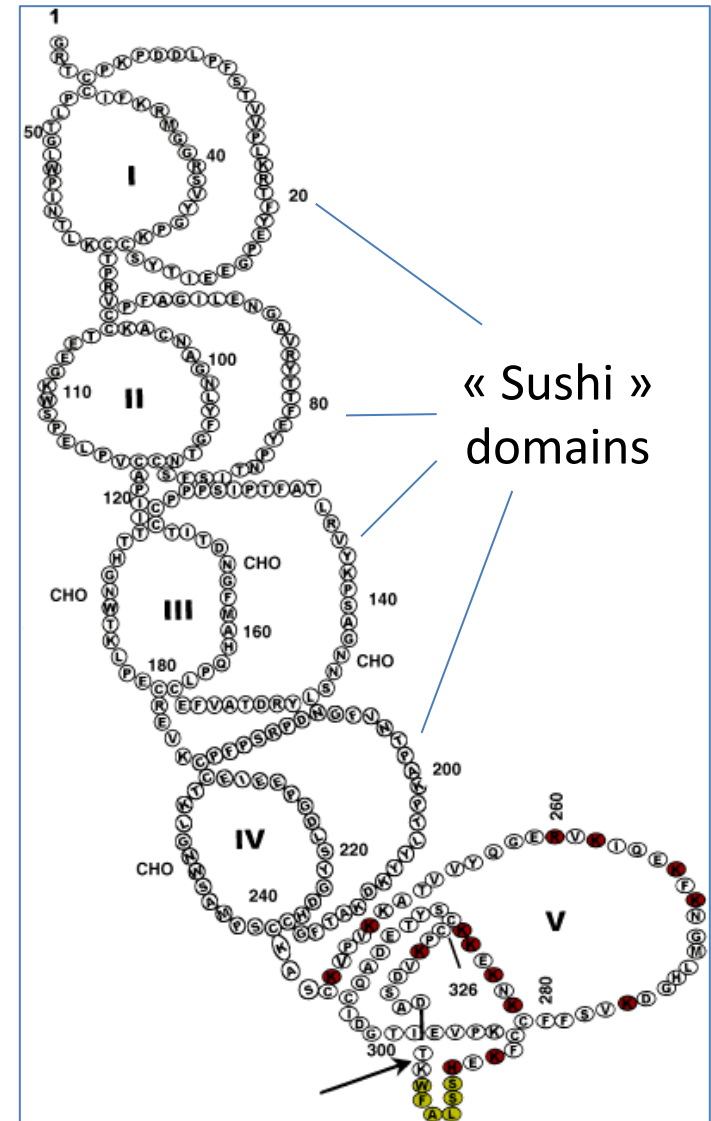
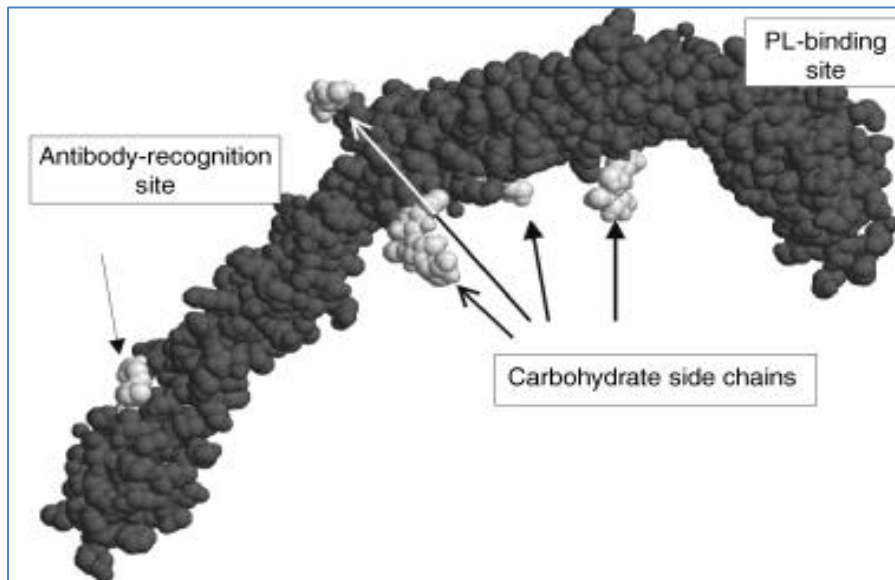
- circulating antiphospholipid antibodies
- thromboembolic events, fetal loss or obstetrical complications such as eclampsia

Antiphospholipid antibodies (APL)

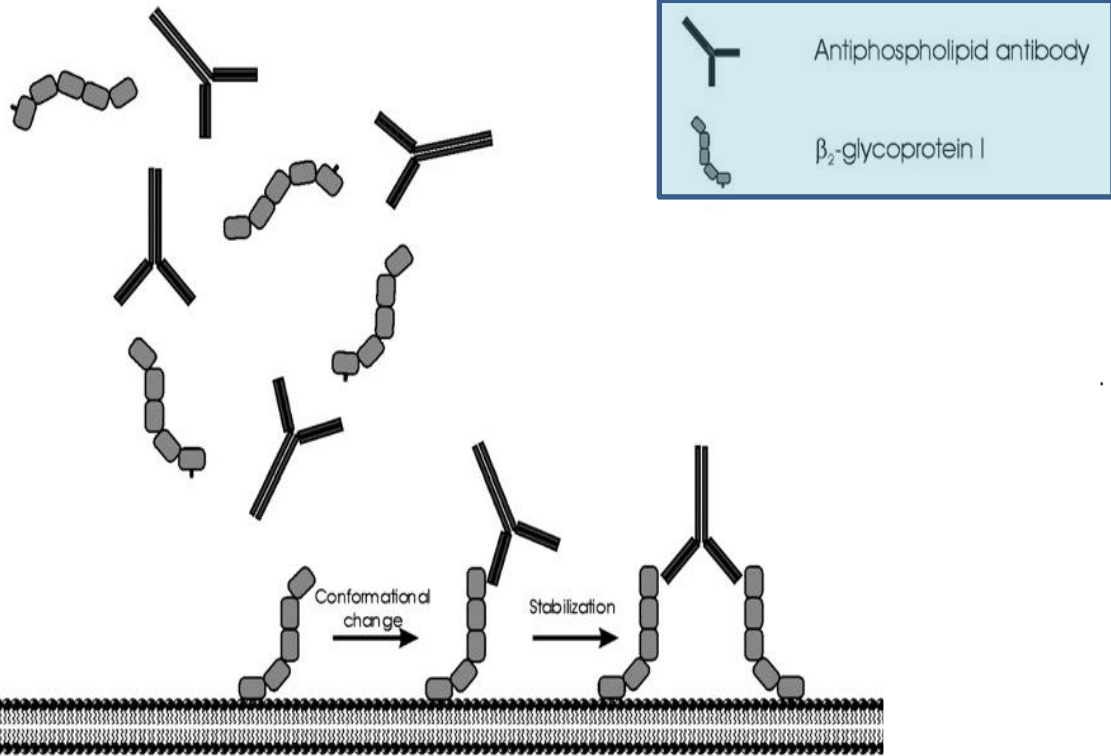
- An heterogeneous family of antibodies reacting with phospholipid-binding proteins.
- **β 2-glycoprotein I** represents the main phospholipid-binding protein.
- Other phospholipid-binding proteins demonstrated as antigenic targets for APL:
 - protein S,
 - protein C
 - prothrombin
 - annexin V
 - annexin II
 - vimentin/cardioliipin complex¹

β_2 -glycoprotein I

- Plasma glycoprotein of 50 kD (plasmatic concentration: 200 $\mu\text{g}/\text{mL}$)
- Member of the complement control protein family (“sushi” domains)
- Binds anionic phospholipids
 - WEAK binding under physiological conditions
- Inherited deficiency is not a risk factor for thrombosis

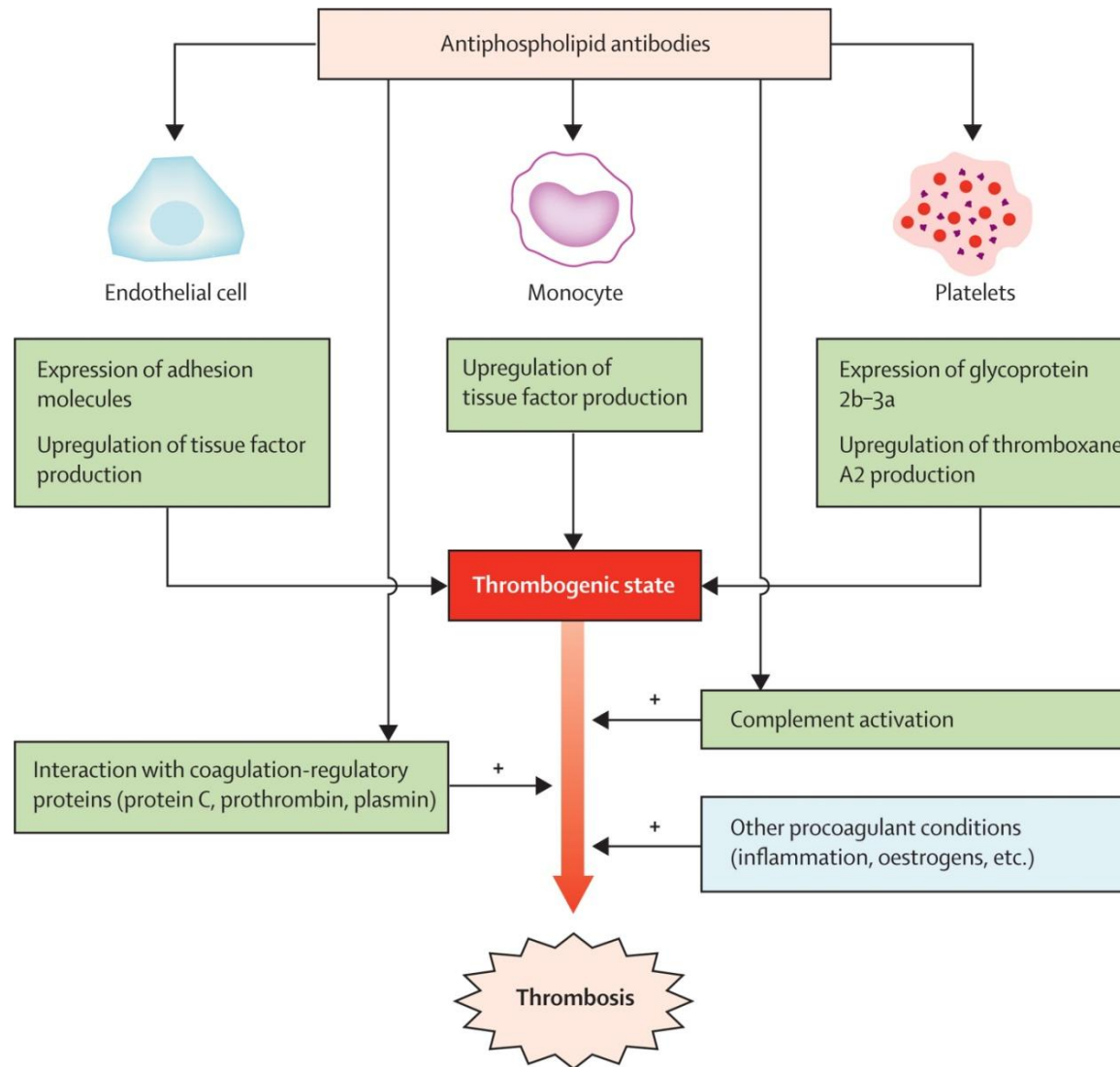


Damage occurring at the cell surface of an APS patient with antibodies against epitope G40-R43 on domain I of β_2 -glycoprotein I



β_2 -glycoprotein I initially binds the anionic phospholipids with a rather low affinity. Following binding, it undergoes a conformational change that enables the antibody to bind the epitope G40-R43 of two β_2 -glycoprotein I molecules.

Pathogenesis of thrombosis in APS



Clinical manifestations of APS

Frequent (>20% of cases)

- Venous thromboembolism
- Thrombocytopenia
- Miscarriage or fetal loss
- Stroke or transient ischaemic attack
- Migraine
- Livedo reticularis

Less common (10–20% of cases)

- Heart valve disease
- Pre-eclampsia or eclampsia
- Premature birth
- Haemolytic anaemia
- Coronary artery disease

Unusual (<10% of cases)

- Epilepsy
- Vascular dementia
- Chorea
- Retinal artery or vein thrombosis
- Amaurosis fugax
- Pulmonary hypertension
- Leg ulcers
- Digital gangrene
- Osteonecrosis
- Antiphospholipid syndrome nephropathy
- Mesenteric ischaemia

Rare (<1% of cases)

- Adrenal haemorrhage
- Transverse myelitis
- Budd-Chiari syndrome



Revised classification criteria for APS:

Clinical criteria

Vascular thrombosis

- One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.
- Thrombosis should be supported by objective validated criteria—ie, unequivocal findings of appropriate imaging studies or histopathology. For histopathological support, thrombosis should be present without substantial evidence of inflammation in the vessel wall.

Pregnancy morbidity, defined by one of the following criteria:

- One or more unexplained deaths of a morphologically healthy fetus at or beyond the 10th week of gestation, with healthy fetal morphology documented by ultrasound or by direct examination of the fetus.
- One or more premature births of a morphologically healthy newborn baby before the 34th week of gestation because of: eclampsia or severe pre-eclampsia defined according to standard definitions or recognised features of placental failure.
- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of patients according to one of the three criteria.

- **Heart valves pathology:**
11,6% of patients with APS, independently from SLE
- **Livedo:**
increased prevalence if SLE, sexe F
- **Thrombocytopenia** (platelets < 100 G/l, confirmed 12 weeks later):
 - prevalence 20-40%
 - for diagnosis and treatment cf. ITP
 - ITP + APL: more thrombotic events, 5 years follow-up
 - exclusion of other causes of thrombocytopenia
- **Nephropathy**

Revised classification criteria for APS: Laboratory criteria

- Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid-dependent antibodies).
- Anticardiolipin antibody of IgG or IgM isotype, or both, in serum or plasma, present in medium or high titres (ie, >40 GPL or MPL, or greater than the 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA.
- Anti- β 2-glycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titres greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

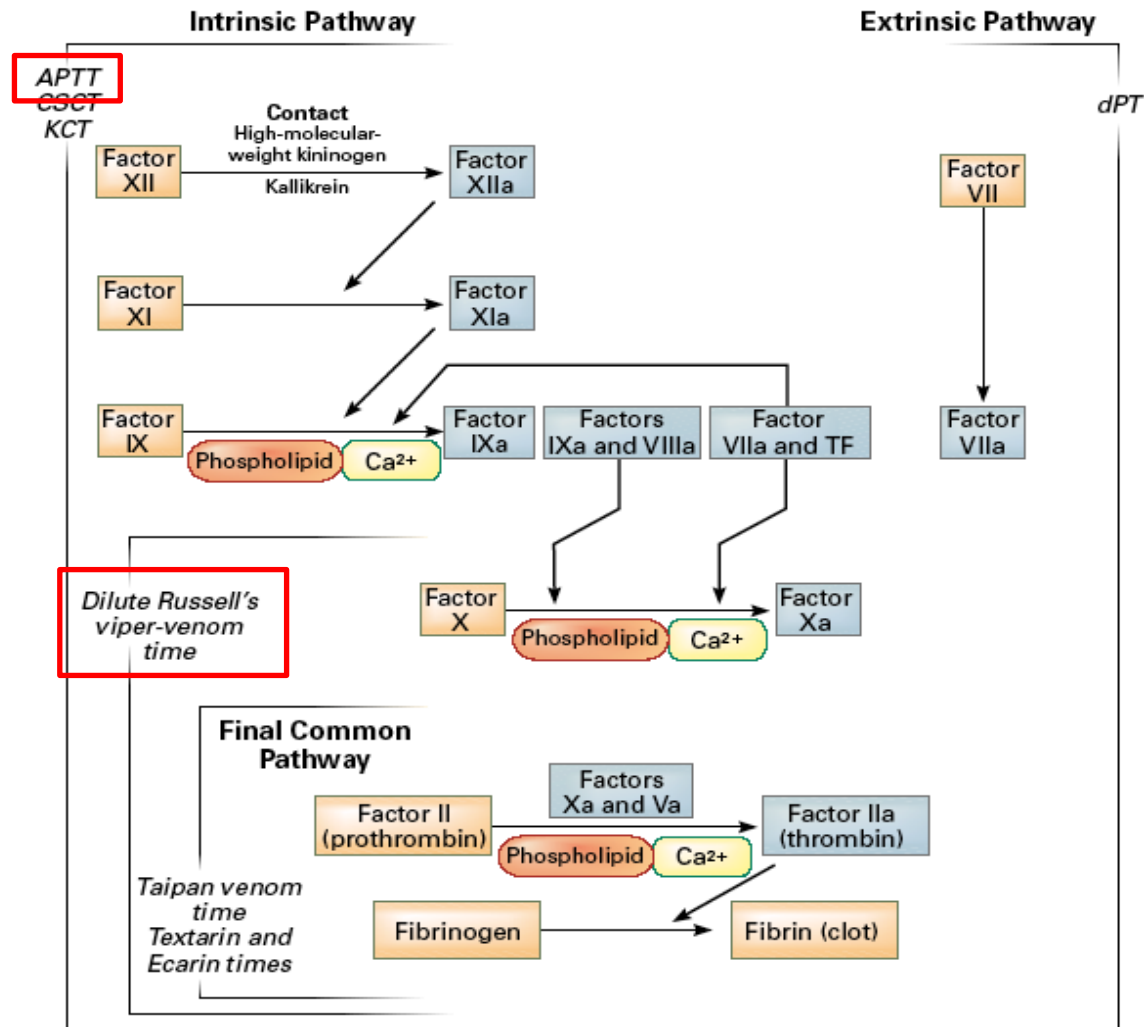
Classification

- I > 1 criteria
- IIa LA alone
- IIb ACL alone
- IIc anti- β 2GP1 alone

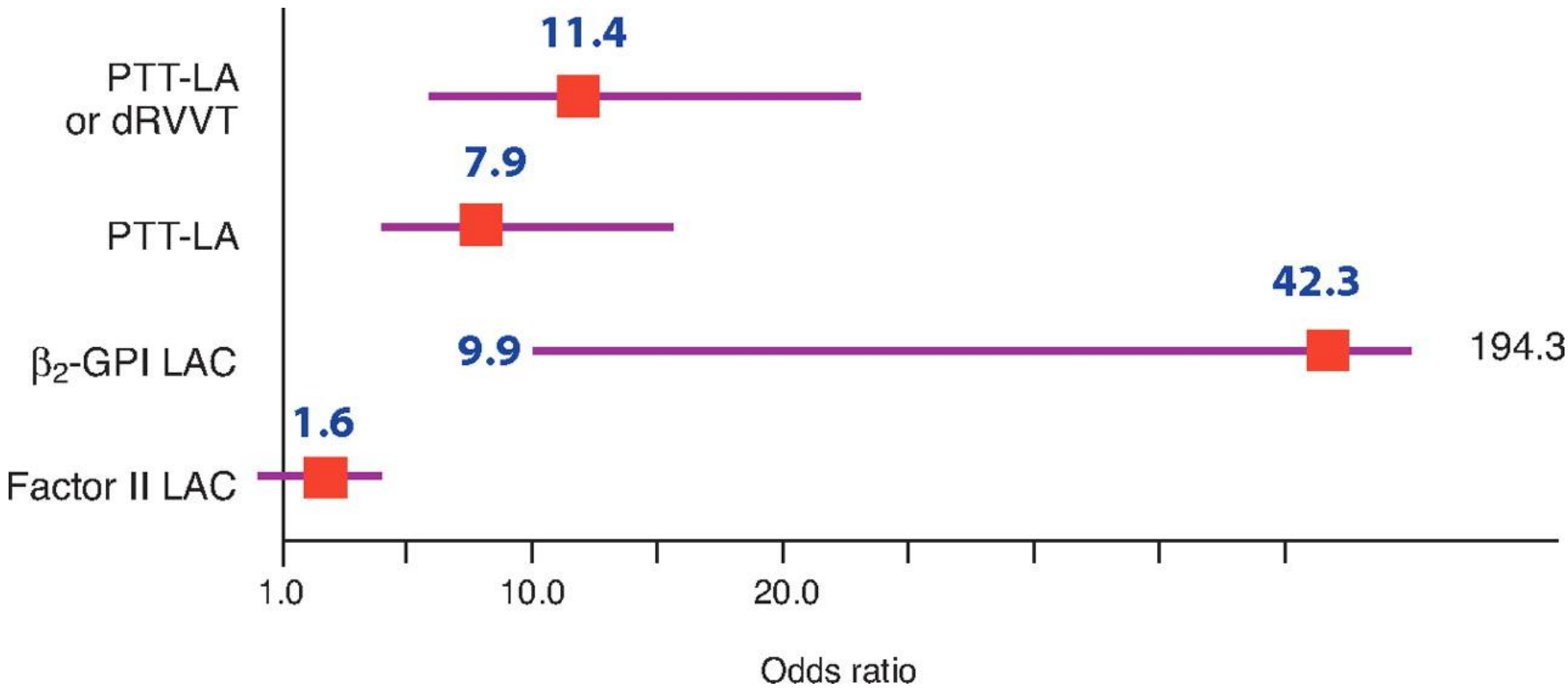
Minimum 12 weeks between clinical symptoms and laboratory tests

Do not perform laboratory test >5 years after clinical manifestations

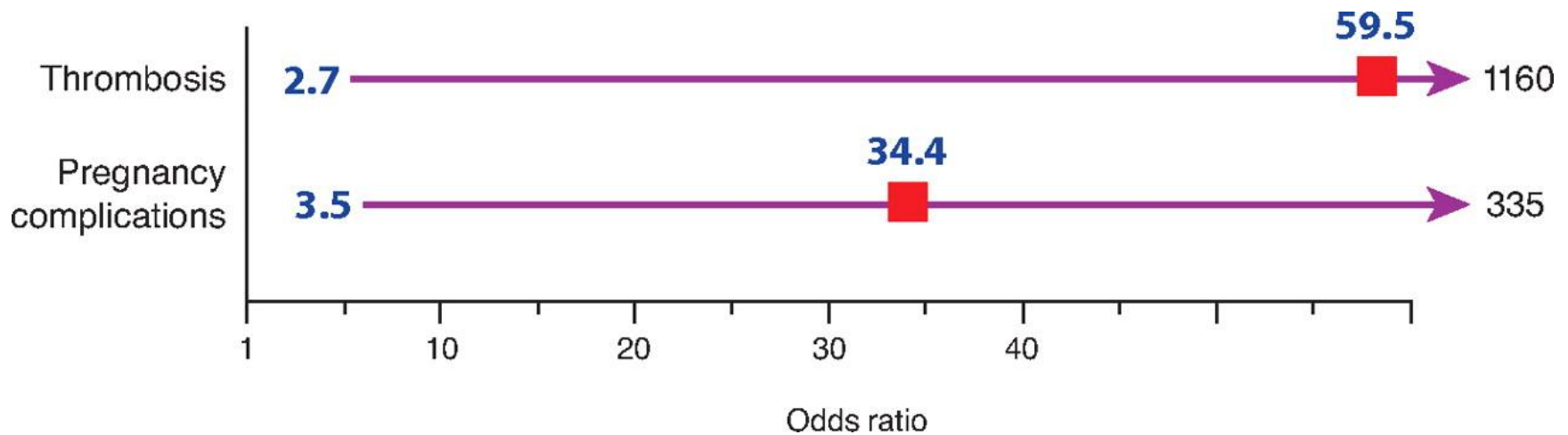
Detection of Lupus anticoagulant antibodies by in vitro coagulation assays



β 2-glycoprotein I -dependent LAC strongly associates with thrombosis, compared with factor II (prothrombin)-dependent LAC



Positivity on multiple assays (LAC/CL-ELISA/direct β 2-glycoprotein I - ELISA) is associated with an increased risk of thrombosis and pregnancy complications



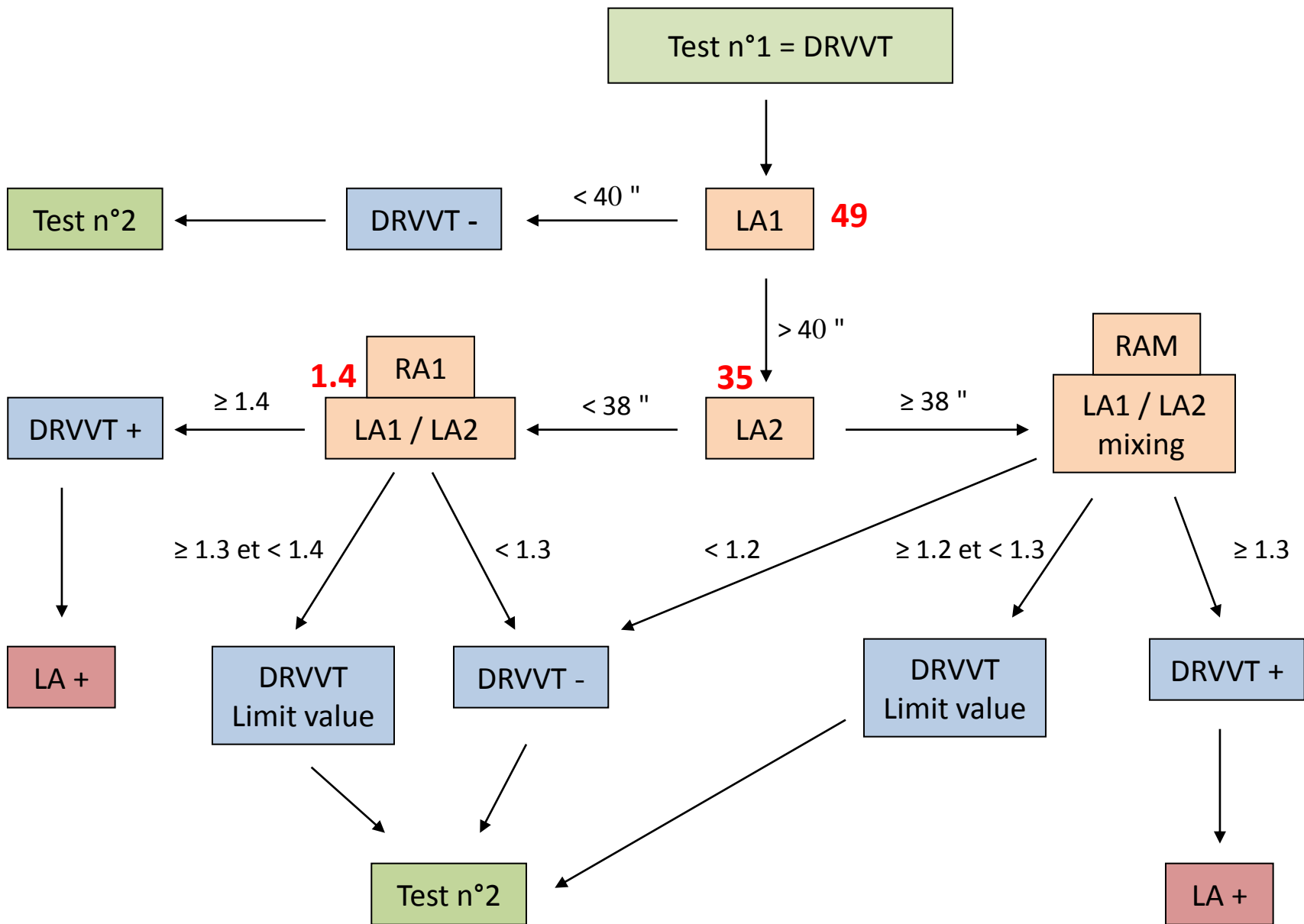
Case #1

26-year-old woman

Lupus, PT 75% one year ago.

Please comment these lab findings:

- PT 20 % 80-120
- aPTT 38 sec. 20-30
- Fib. 2,2 g/l 2,0-4,0
- Facteur II 36 % 80-150
- Facteur V 13 % 70-180
- Facteur VII 25 % 70-180
- Facteur X 11 % 75-170
- Factor VIII 46 % 65-170
- Factor XI 11 % 75-170



Additional tests

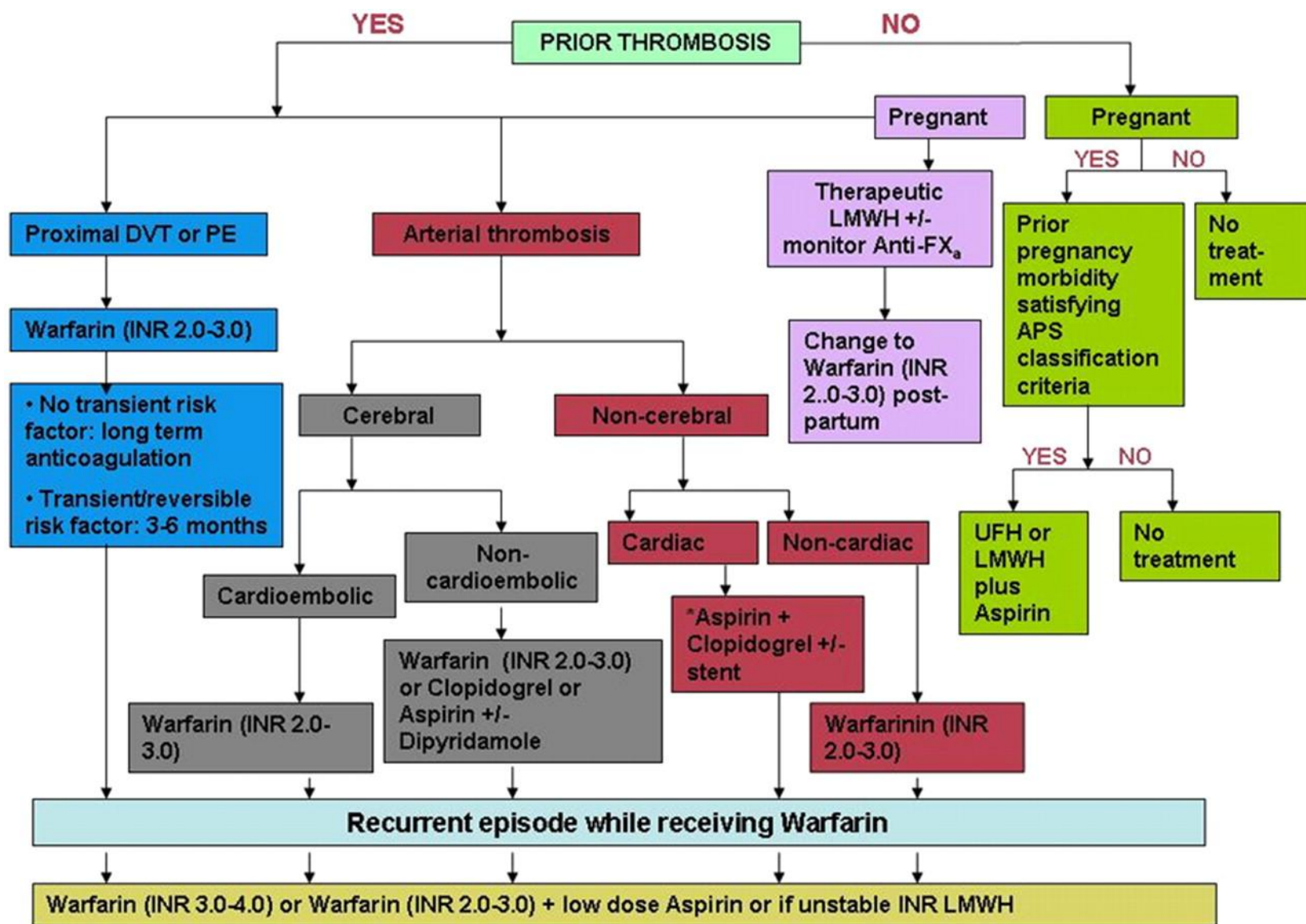
Anticardiolipin Ab

- Screening test +
- IgG 18 GPL <15
- IgM 2300 MPL < 12.5

Anti-β2-GP1 Ab

- Screening test +
- IgG 2 SGU <20
- IgM 79.5 SMU <20

Treatment algorithm for the thrombotic and obstetric complications associated with persistently positive antiphospholipid antibodies



Secondary prophylaxis	
Patients with definite antiphospholipid syndrome and first venous event*	Indefinite anticoagulation to a target INR 2.0–3.0
Patients with definite antiphospholipid syndrome and arterial event*	Indefinite anticoagulation to a target INR 3.0–4.0 or combined antithrombotic treatment
Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2.0–3.0	Indefinite anticoagulation to a target INR 3.0–4.0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin
Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for deep vein thrombosis treatment
Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for arterial thrombosis

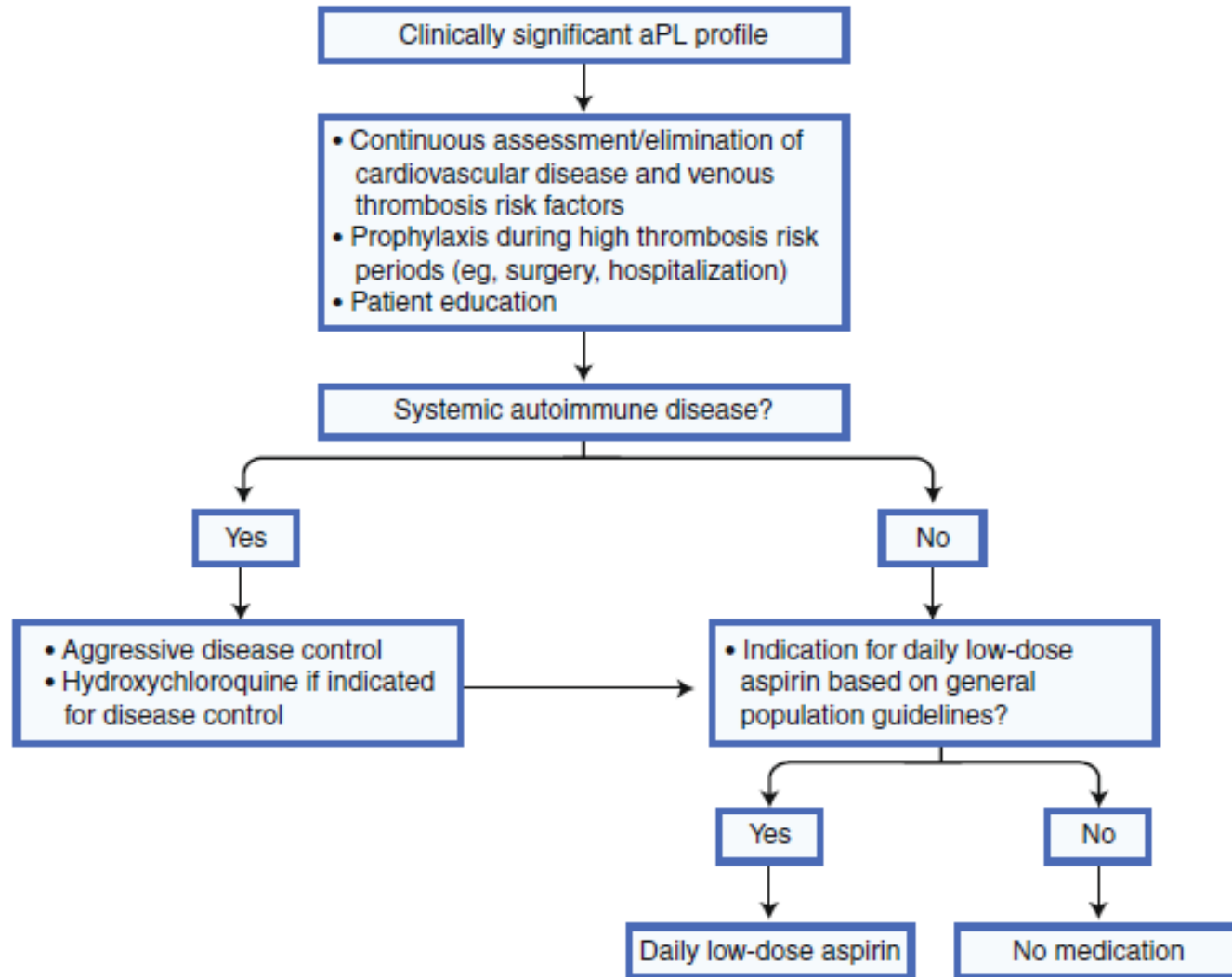
INR=international normalised ratio. *Less aggressive or long-lasting antithrombotic treatments might be appropriate in low-risk patients.

Table 1: Recommendations for secondary prophylaxis in patients with antiphospholipid antibodies and thrombosis

Primary thromboprophylaxis	
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
All patients with antiphospholipid antibodies	Strict control of vascular risk factors
High-risk situations (surgery, post partum, long-lasting immobilisation)	Adequate thromboprophylaxis

Table 2: Primary thromboprophylaxis in patients with antiphospholipid antibodies

Proposed primary thrombosis prophylaxis algorithm for patients with clinically significant APL profiles



Regimen

Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage

Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)

Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency

Low-dose aspirin plus:

- Unfractionated heparin (7500–10 000 IU subcutaneously every 12 h in the first trimester; 10 000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1.5 times the control mean)
- LMWH (usual prophylactic doses)

Antiphospholipid syndrome with thrombosis

Low-dose aspirin plus:

- Unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the mid-interval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range)
- LMWH (usual therapeutic dose—eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1.5 mg/kg/day subcutaneously, or dalteparin 200 U/kg/day subcutaneously)†

aPTT= activated partial thromboplastin time. LMWH=low-molecular-weight heparin. *Women without a lupus anticoagulant in whom the aPTT is normal can be monitored with the aPTT. Women with lupus anticoagulant should be monitored with antifactor Xa activity. †Need for dose adjustments over the course of pregnancy remains controversial.²⁹ Some experts argue that in the absence of better evidence, it is prudent to monitor anti-factor Xa LMWH concentrations 4–6 h after injection with dose adjustment to maintain a therapeutic antifactor Xa concentration (0.6 to 1.0 U/mL if a twice-daily regimen is used; slightly higher if a once-daily regimen is chosen).

Table 3: Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy

Case #2

36 year-old woman

- Death in utero (16 weeks of pregnancy) 18 years ago
- Death in utero (28 weeks of pregnancy) 11 years ago
- Pregnancy w/o complications 8 years ago (full dose AC), β 2-GP1 IgG Ab 2 times pos. (diagnosis of APS)
- DVT (lower right limb) and PE 3 years ago
AVK: INR 2-3
- Obesity BMI 50 kg/m²
Gastric bypass 2 years ago
- APL Ab: multiple tests, all neg.

What do you suggest for the next pregnancy? Does the patient have APS? What about long term AC?

Case #3

31 year-old woman

- ITP diagnosed 3 years ago (platelet count 80 G/L)
- Spontaneous abortion 10th week of gestation 4 years ago
- Death in utero (16th week of pregnancy) 3 years ago
- Placenta: increase of fibrin (subchorial, peri-villous)

- Pregnancy 10th week of gestation
- Multiple APL tests: neg., thrombophilia screening neg., platelet 30 G/L

What is your diagnosis? What do you suggest?