Lupus related diseases:

- Antiphospholipid syndrome
- Drug induced lupus
- Neonatal lupus

Antiphospholipid syndrome:

Diagnosis of the anti-phospholipid syndrome (APS) requires that a patient have both a **clinical event** (thrombosis or pregnancy morbidity) and the **persistent presence of the anti-phospholipid antibody (aPL)**, documented by a solid phase serum assay.

The prevalence of positive aPL tests increases with age. Ten percent to 40% of patients with SLE and approximately 20% of patients with rheumatoid arthritis have positive aPL tests; however, the incidence of APS is relatively low.

Twenty percent of women who have experienced three or more consecutive fetal losses have aPL.

ETIOLOGY

The main antigen to which aPLs bind is not a phospholipid but rather a phospholipid-binding plasma protein, namely, β2-glycoprotein 1 (β2-GP1). ß2-GP1 may function in the elimination of apoptotic cells and as a natural anticoagulant.

Criteria for diagnosis: (clinical and laboratory)

Clinical Criteria

1. Vascular thrombosis

One or more clinical episodes of **arterial**, **venous**, or **small vessel** thrombosis in any tissue or organ

2. Pregnancy morbidity

(a) One or more unexplained deaths of a **morphologically normal** fetus at or beyond the 10th week of gestation,

Or

(b) One or more premature births of a **morphologically normal neonate** before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or recognized features of placental insufficiency.

Or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with exclusion of maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes

Laboratory Criteria

1. Lupus anticoagulant present in plasma on **two or more occasions at least 12 weeks** apart.

2. Anti-cardiolipin antibody of IgG or IgM isotype in serum or plasma, present in medium or high titer on **two or more occasions at least 12 weeks** apart.

3. Anti–β-2-glycoprotein I antibody of IgG or IgM isotype in serum or plasma present on **two or more occasions at least 12 weeks apart**.

‡Superficial venous thrombosis is not included in the clinical criteria.

Other Features Suggesting the Presence of Anti-phospholipid Antibodies syndrome:

Clinical

Livedo reticularis

Thrombocytopenia (usually 50,000-100,000 platelets/mm3)

Autoimmune hemolytic anemia

Cardiac valve disease (vegetations or thickening)

Multiple sclerosis–like syndrome, chorea, or other myelopathy, non-focal neurologic symptoms such as lack of concentration, forgetfulness, and dizzy spells

Laboratory

IgA anticardiolipin antibody

IgA anti–β-2-glycoprotein I

CLINICAL FEATURES

Thrombosis: Deep vein thrombosis and stroke are the most common clinical manifestations of APS.

Unusual anatomic locations (Budd-Chiari syndrome; sagittal sinus and upper extremity thromboses).

Renal thrombotic microangiopathy, glomerularcapillary endothelial cell injury, and thrombosis of renal vessels cause proteinuria **without cells in the urine or hypocomplementemia** and may lead to severe hypertension, renal failure, or both.

INVESTIGATIONS:

Prolonged phospholipid dependent coagulation screening test (PTT)

Anti-nuclear and anti-DNA antibodies occur in approximately 45%

Thrombocytopenia in APS is usually modest (>50,000/mm3);

Imaging Studies

MRI shows vascular occlusion and infarction consistent with clinical symptoms

Echocardiography or cardiac MRI may show severe Libman-Sacks endocarditis and intracardiac thrombi

TREATMENT:

Treatment Recommendations for Persons Persistently Positive for Anti-phospholipid Antibody

Clinical Features	Recommendation
• Asymptomatic	No treatment
• Venous thrombosis	Warfarin INR 2-3 indefinitely
• Arterial thrombosis	Warfarin INR 2-3 indefinitely
• Recurrent thrombosis	Warfarin INR 3-4 ± low-dose aspirin

Pregnancy:

• First pregnancy	No treatment
• Single pregnancy loss at<10 wk	No treatment
• ≥1 Fetal or ≥3 (pre)-embryonic losses→Prophylactic heparin +low-dose aspirin throughout pregnancy	

- Thrombocytopenia >50,000/mm3 No treatment
- Thrombocytopenia <50,000/mm3 Prednisone, IVIG

Aspirin is the standard of care after an ischemic stroke or a transient ischemic attack.

Clinical experience suggests that thrombolytic agents for acute thrombosis are not helpful because reocclusion occurs rapidly.

DRUG-INDUCED LUPUS

Drug-induced lupus is the presence of SLE manifestations occurring after exposure to specific medications. Drug-induced lupus affects males and females equally and is unlikely to cause significant renal or CNS disease.

Hepatic involvement in drug-induced lupus is common. Similar to SLE, include fever and/or other constitutional symptoms, arthritis/arthralgias, myalgias, serositis are common.

Anti–dsDNA antibodies hypocomplementemia are less likely to occur in drug-induce lupus.

Drugs Implicated in Drug-Induced Lupus

- **Hydralazine**
- **Procainamide**
- **Minocycline**
- **Isoniazid**
- **Hydrazine**

Virtually all patients with DIL will have a positive ANA

Antihistone antibodies IgG: these are the most common of autoantibody specificity in DIL.

Antibodies to histones are also frequent in **idiopathic SLE**, detectable in 50% to 80% of patients,

Some patients taking either procainamide or hydralazine will have a positive test but not symptoms of lupus-like disease.

Positive ANA may persist for a prolonged time (>1 year) even after symptoms resolve.

NEONATAL LUPUS

NLE is a passive autoimmune condition caused by transfer of circulating maternal autoantibodies to the fetal circulation.

The maternal autoantibodies associated with the vast majority of NLE cases are anti-Ro/SS-A (or anti-SSA) and anti-LA/SS-B (or anti-SSB); however, anti-UA RNP antibodies have been described in NLE. NLE develops in only 1% to 2% of children born to mothers with these circulating antibodies.

Inflammatory changes related to NLE resolve when maternal autoantibodies are cleared from the infant's circulation, typically within 6 months.

Noncardiac NLE manifestations are reversible and usually do not require any treatment.

Congenital heart block and cardiomyopathy can cause death and morbidity.

The clinical manifestations of NLE include: (cutaneous, hepatic, neurology, hematology and cardiac)

Cardiac conduction abnormalities can present in utero (starting at 16 weeks of gestation when maternal Igs can cross the placenta) or shortly after birth and include conduction system abnormalities ranging from prolongation of the PR interval to complete heart block.

Given the risk for NLE, it is recommended that pregnant women with circulating anti-Ro/SSA or anti-La/SSB antibodies undergo monitoring of fetal P-R interval and cardiac function during pregnancy beginning at 16 weeks. Mothers with antibodies to Ro/SS-A or La/SS-B should have serial fetal echocardiography weekly from 16 to 26 week and every 2 weeks thereafter until 34 weeks.

Dexamethasone (4 mg/ day) or betamethasone (4 mg/day) are not metabolized substantially by the placenta and therefore cross into the fetal circulation and these drugs should be used early for prevention of CHB. No therapy has been proven effective in reversing complete heart block once it is established.