Chapter from the book *Antiphospholipid Syndrome*

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Antiphospholipid Syndrome in Pregnancy

Kjell Haram¹, Eva-Marie Jacobsen²,³ and Per Morten Sandset²,³

¹Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen
²Department of Haematology, Oslo University Hospital Rikshospitalet, Oslo
³Institute of Clinical Medicine, University of Oslo, Oslo
Norway

1. Introduction

The antiphospholipid syndrome (APS) is a multisystemic disease, characterized by venous or arterial thromboses, or certain obstetric complications, and the presence of antiphospholipid antibodies (APAs)⁴. APAs are a heterogeneous group of autoantibodies that bind to negatively charged phospholipids, phospholipid-binding protein, or a combination of the two. Lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies are the main antibodies in this syndrome⁵. APS occurs in isolation as a primary APS in more than 50% of the cases, but can be associated with other autoimmune diseases, most often with systemic lupus erythematosus (SLE). Twenty to 35% of women with SLE develop APS⁶. APS occurs for the most part in young women of fertile age⁷. It occurs rarely in children, and only 12% of all APS occur after 50 years of age⁸.

2. Antiphospholipid antibodies in pregnancy

Antiphospholipid antibodies in pregnancy are associated with recurrent miscarriage, intrauterine growth restriction (IUGR), preeclampsia, placental abruption, premature delivery or fetal death in addition to arterial or venous thrombosis⁹. Thus, the woman may experience both early and late fetal loss. Vascular thrombosis can occur in any organ or tissue. Deep vein thrombosis in the legs is most frequent, but the renal vein, the pulmonary vein, the inferior vena cava and the hepatic and portal vein may also be affected. The most common site of arterial thrombosis is the cerebral circulation, but occlusion of coronary and retinal arteries has also been reported⁸. APA, particularly LA, is an independent risk factor for first and possibly recurrent ischemic stroke in young adults¹⁰. Cerebral ischemic events can occur in any vascular territory¹¹. Cerebral angiography typically demonstrates intracranial branch or trunk occlusion or is normal in about one third of patients so studied¹². In addition, leg ulcer, chorea, and migraine have been associated with APAs⁵. A wide range of abdominal manifestations have been reported in APA-positive patients. Hepatic involvement is most numerous, thereafter thrombotic events in branches of the intestinal vasculature¹³.
3. Diagnosis of APS in non-pregnant and pregnant women

According to the last updated consensus the diagnosis of obstetric APS needs to be based on: 1) one or more unexplained deaths of normal fetuses at or beyond the 10th week of gestation, or 2) one or more premature births before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency, or 3) three or more unexplained consecutive spontaneous abortions before the 10th gestational week. Pregnant women with such complications should have laboratory testing.

The diagnosis of APS must be based both on clinical criteria and persistent positivity for APA. Laboratory testing for APA is used to confirm or refute the diagnosis. Thrombosis must be confirmed by strict objective criteria (angiography, venography, Doppler ultrasound examination or CT). CT is considered to be first-line investigation of suspected thrombosis in patients with abdominal symptoms. CT features of mesenteric ischemia are thickening of both small and large bowel walls with prominence of the supplying mesenteric vessels. For histopathological confirmation thrombosis should be present without evidence of inflammation in the vessel wall. Cerebral thrombosis can be diagnosed by cerebral angiography, transcranial Doppler technique, or magnetic resonance imaging (MRI). In some cases, MRI has revealed small foci of high signal in subcortical white matter scattered throughout the brain.

4. Venous thromboembolism

Pregnancy is a risk factor for venous thromboembolism (VTE). From two to ten-fold increase of VTE compared with the risk for non-pregnant women has been reported. The risk of thrombosis in the lower extremities may be even higher in women with coexisting risk factors (e.g. obesity, thrombophilia or acquired APS). Women with APS are at high risk of recurrent thrombosis, and this risk may even be higher in pregnant women. A retrospective comparison of the overall risk of recurrence of VTE revealed risk of 11% per 100 patient-years during pregnancy and 3.7% in the non-pregnant state (the risk ratio for VTE during pregnancy was 3.5 with 95% confidence interval (CI) 1.6-7.8). Although a clear association between APAs and vascular events has been described, the data from a cohort study did not support that aCL antibodies affect vascular mortality.

5. Catastrophic APS

Catastrophic APS (CAPS), also known as “Asherson’s syndrome”) is an unusual (<1%) variant of APS, which is characterised by rapid appearance of multiple thromboses (mainly small-vessel thrombosis) that lead to multiorgan failure. It is an acute, life-threatening, complication which may occur both in non-pregnant and pregnant women.

Diagnostic algorithms which have been proposed include the occurrence of new thromboses in at least three different organs in less than a week. In patients with a history of APS or persistent APA-positivity as described in the guidelines, a diagnosis of definite CAPS is made if the patient has new thrombosis in at least three organs, with micro-thrombosis confirmed by biopsy. If only two organs are affected, or if confirmation with biopsy is not available, a diagnosis of probable CAPS is made. If the patient does not have a history of APS or persistent APA-positivity, APA-positivity must be confirmed twice with at least 12 weeks apart.
Disseminated intravascular coagulation occurs in approximately 25% of patients with CAPS(30). In more than 50% of the cases, catastrophic events are triggered by infections, trauma or surgery, anticoagulation withdrawal, malignancies, lupus “flares” or obstetric complications(28).

CAPS may infrequently appear during pregnancy after a Caesarean section or fetal loss(28). The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) may be part of the catastrophic syndrome(31). Bone marrow necrosis and a refractory HELLP syndrome have been reported in a woman with catastrophic APS. The fetus died in spite of termination of pregnancy(32). A retrospective study comprised 15 cases of catastrophic APS in pregnancy or puerperium. APS was primary in 7 while 8 had SLE or lupus-like disease. In 8 of 15 cases (53%) the catastrophic syndrome were associated with HELLP syndrome. Six cases (43%) occurred in the puerperium and 1 after fetal death(28).

**Laboratory testing**

Transient occurrence of APA may not be associated with increased risk for clinical events. Therefore, it is essential that a positive test for APA is repeated after at least 12 weeks to confirm diagnostic criteria(7).

LA assays are functional assays based on one of several phospholipid-dependent clotting tests(10). LA seems to be the most specific test for APS(33). LA is strongly associated with fetal loss at more than 10 weeks’ gestation. In a metaanalysis on women without autoimmune disease, LA was associated with late recurrent fetal loss (at least 2 fetal losses) with odds ratio 7.8 (95% CI 2.3-26.5)(34). Positive tests for APAs are found in 2% of the general population and in 30-40% of patients with SLE(12,35). In general obstetric clinics the prevalence of APAs has been reported to be between 2.7% and 7%(36).

aCL antibodies are detected by enzyme linked immunosorbent assays (ELISAs) that measure anti-β2GP1 antibody dependent IgG and IgM aCL antibodies(2,7,37). The aCL ELISA test has high sensitivity, but low specificity(8) and skill and experience are necessary in interpreting the results(4). Despite international efforts to standardize laboratory testing significant variation in the performance of APS antibody assays in laboratories remains a critical problem(2).

In 1990 three independent groups reported that aCL antibodies were directed against the plasma protein β2GP1(38-40). Several commercial ELISA assays for the detection of anti-β2GP1 antibodies of IgG and IgM type have later been developed. However, the laboratory detection of APAs by ELISA tests has been flawed by lack of standardisation and discordant results between manufacturers and laboratories(41). The European Forum on Antiphospholipid Antibodies have published methodological analyses and proposals for the performance of these assays(42,43).

To exclude the presence of APAs, both clotting-based assays for LA and ELISA tests for anti-β2GP1/aCL should be performed(7). LA-testing should be performed according to guidelines published as an official communication of the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis(44). The latest consensus on classification criteria for APS states that cut-off for positive aCL and/or anti-β2GP1 tests should be >99th percentile of the titres in a reference group or, for aCL antibodies, should be present in medium or high titre (>40 IgG or IgM phospholipid units)(7).
6. Thrombocytopenia in patients with APS

APS related thrombocytopenia is defined by a platelet count less than \(100 \times 10^9/L\), confirmed twice 12 weeks apart, and is found in approximately 20% of patients with APS and in more than 40% of patients who have APS associated with underlying SLE\(^{(45)}\). A minority of patients have thrombocytopenia with platelets less than \(50 \times 10^9/L\). APS-associated thrombocytopenia is an autoimmune phenomenon and its relation to thrombotic risk is poorly characterized. However, thrombocytopenia does not appear to reduce thrombotic risks in patients with APS\(^{(45)}\).

7. Distinguishing APS from other prothrombotic and thrombocytopenic conditions

The differential diagnosis in patients presenting with thrombocytopenia includes thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and DIC\(^{(45)}\). Distinguishing these conditions can be challenging. Diagnosing APS requires documentation of persistent APA antibodies in combination with compatible clinical features of thrombosis or pregnancy morbidity. However, APA antibodies have been documented in TTP and other thrombotic microangiopathies including haemolytic uremic syndrome and HELLP syndrome\(^{(16)}\), as well as in cases of HIT. Patients with TTP present with microangiopathic hemolytic anaemia, typically manifesting with schistocytes on the blood smear and evidence of hemolysis, which is not a typical feature in APS. Measurement of the ADAMTS-13 metalloprotease, if available, may be helpful in these situations given that TTP is associated with ultra-large von Willebrand factor multimers that result from a deficiency in ADAMTS-13. If the patient is under medication with heparin, HIT must be considered. Notably, false-positive HIT antigen tests can be distinguished from true HIT antibodies by using enzyme immunoassays for PF4/heparin complexes tested with heparin excess or with use of functional assays\(^{(46)}\). Patients with DIC typically have negative tests for APAs, frequently with evidence of thrombocytopenia, coagulopathy and thrombotic or hemorrhagic complications\(^{(45)}\). Patients with severe DIC have low platelet count, fibrinogen and antithrombin (consumption coagulopathy).

8. Thrombotic microangiopathic hemolytic anaemia (TMHA) and APS

The term thrombotic microangiopathic hemolytic anaemia (TMHA) was introduced by Symmers in 1952 to describe clinical disorders related to the presence of localised or diffuse microvascular thrombosis\(^{(47)}\). TMHA is characterised by thrombocytopenia, microangiopathic hemolytic anaemia (as indicated by erythrocyte fragmentation on peripheral blood smears) accompanied by a negative Coombs’ test, fever, neurological symptoms, and kidney involvement\(^{(48)}\). Several reports have pointed out the relationship of TMHA with the presence of APAs\(^{(48)}\). SLE was the first autoimmune disease in which the association of TMHA with APA was recognised\(^{(48)}\). There is evidence to support the hypothesis that TMHA might be a manifestation of APS\(^{(48)}\).

9. APS, preeclampsia and the HELLP syndrome

A systematic literature search for the association of aCL antibodies with preeclampsia generated 68528 abstracts and 64 full-text articles \(^{(7)}\). Inclusion criteria were cohort-, case-
control or controlled cross-sectional-studies comprising women with no autoimmune diseases but with IgG or IgM aCL antibody of at least 20 units, or both, with preeclampsia as endpoint. Twelve studies were included in a meta-analysis. The study comprised publications from before 2006 (when new criteria were established) and thus did not consider the latest antiphospholipid criteria when addressing aCL cut-off levels in the final analysis\(^7\). Different methods of diagnosing preeclampsia were used in these 12 publications. The severity of preeclampsia was not stated in 7 of the publications. Pooled OR for association of aCL antibodies with preeclampsia was 2.9 (95% CI 1.4-5.9)\(^5\). Pooled OR for aCL antibodies and severe preeclampsia was 11.2 (95% CI 2.7-46.8). It was concluded that moderate-to-high levels of aCL antibodies were associated with preeclampsia. There was, however, insufficient evidence to advocate use of aCL antibodies as predictors of preeclampsia\(^5\).

Branch and Khamashta reported in 2003 that in women with SLE and prior thrombosis the median rate of preeclampsia was 32% ranging up to 50%; that of preterm births ranged from 32% to 65%\(^2\). One study suggested that the second trimester Doppler ultrasound examination may be the best predictor of late pregnancy outcome in SLE and/or the APS\(^49\).

Women with APAs seem to have increased risk of developing a HELLP syndrome\(^31;50-52\). One series, that comprised 75 pregnancies with primary or secondary APS, included 7 women who had 8 episodes of HELLP\(^53\). A retrospective analysis of 16 episodes of HELLP complicating APS comprised 15 women. APS was primary in 9 women and secondary in 6 cases\(^31\). The HELLP syndrome was complete in 10 episodes and partial in 6, occurring in the second trimester (44%) in 7 cases (the earliest at 18 weeks’ gestation), and 12.5% at 18-20 weeks\(^31\). The outcome was 8 live births, 2 stillbirths and 6 fetal deaths\(^31\). Backos et al. reported two cases of a HELLP syndrome in a series of 150 pregnancies in women with recurrent miscarriages and APAs\(^54\). In a placebo controlled study of intravenous immunoglobulin treatment for APS, Branch et al. observed that 6 out of 16 women with APA developed severe preeclampsia and/or HELLP\(^55\). In a literature review of well described cases of HELLP complicating APS, HELLP occurred before 27 weeks’ gestation in most cases. The HELLP syndrome occurred as early as the 8th week of gestation\(^56\). Thus, HELLP appears to develop earlier in women with APS than in women in the general population. The condition also tends to be more severe\(^31\).

In the cases of HELLP syndrome associated with APS published by Le Thi Thoung et al. no case of liver infarction was observed\(^31\). Pauzner et al., on the other hand, found liver infarcts to be almost always associated with APS in women with a HELLP syndrome\(^56\). Pauzner et al. also reviewed 30 pregnancies in 28 women with pregnancy-associated hepatic infarcts. APA were present in 15 of 16 patients with available data, 16 had typical HELLP syndrome. Almost all patients with hepatic infarcts were APA positive in addition to suffering from complete or atypical HELLP syndrome. Hepatic infarcts occurred at all stages of pregnancy\(^57\). In APA positive women the HELLP syndrome usually occurs during the second trimester of pregnancy; one-third of these develop hepatic infarcts\(^58\).

### 10. Pathogenesis of APS

Habitual abortions (defined as ≥3 spontaneous consecutive pregnancy losses) affect 1-2% of women in reproductive age. Up to 5% of women in reproductive age have ≥2 recurrent
abortions\(^{59}\). APA antibodies have also been implicated in first trimester miscarriage\(^{60}\). Detrimental effects of APA antibodies in women with recurrent abortions is extended to pre-embryonic and embryonic losses\(^{30}\). APA may impair both trophoblast invasion in the decidua and the spiral arteries and the placental hormone production and cause utero-placental insufficiency and fetal loss\(^{30}\).

Serbie et al. examined the products of consumption from early pregnancy failures in women with recurrent fetal loss to investigate the mechanism of pregnancy loss\(^{61}\). There were 31 primary APS-positive, 50 APA-negative, 34 aneuploid and 20 control cases with termination of pregnancy for social reasons at 6-14 weeks gestation. Chorionic villous morphology and frequency of intervillous thrombosis were not different among groups. Normal decidual and endovascular trophoblast invasion in the spiral arteries was identified significantly less frequent in primary APA-positive cases (24%), compared with controls (75%), aneuploid (53%), or APA-negative cases (61%; Z=−3.0, P <0.01)\(^{61}\). Chorionic villous morphology and intervillous thrombosis were not different among the groups. Normal decidual and endovascular trophoblast invasion in spiral arteries was identified significantly less frequent in primary APA-positive cases (24%), than in controls (75%), aneuploid (53%), or APA-negative cases (61%). It was concluded that defective decidual and spiral artery endovascular trophoblast invasion, rather than excessive intervillous thrombosis, is the most frequent histological abnormality in primary APA-positive women with early pregnancy loss\(^{61}\). In recurrent miscarriage with APAs, 20-60% of the aborted fetuses are chromosomally abnormal, and chromosomal anomalies as cause of fetal loss must be considered also in APA positive patients\(^{4,62,63}\).

There is a variety of mechanisms by which APA antibodies may cause pregnancy loss. APA antibodies may interfere with the normal in vivo function of phospholipids or phospholipid-binding proteins that are crucial to regulation of coagulation\(^{2}\). Tissue factor (TF), the major cellular initiator of the coagulation protease cascade, plays important roles in both thrombosis and inflammation\(^{64}\). In-vitro studies have shown that certain APAs, specifically those directed against \(\beta_2\)GP1, induce expression of TF\(^{37,65}\). APAs also dysregulate the fibrinolytic system by cross-linking with annexin II (profibrinolytic endothelial cell surface receptor) on the endothelial cell surface inducing increased expression of TF\(^{64}\). Autoantibodies have a causative role in monocyte TF expression. Growing evidence suggests that APA-dependent induction of TF activity on circulating blood monocytes is an important mechanism of hypercoagulability in APS\(^{64}\). TF acting as an pro-inflammatory molecule enhances neutrophil activity which may cause trophoblast injury, placental dysfunction and damage to the embryo\(^{64}\). Activated neutrophiles release reactive oxygen species and proteolytic enzymes leading to decidual damage\(^{64}\). Complement C3 and C5 play a role in APA-induced thrombosis\(^{64}\). In vitro and animal studies have shown that APAs can bind directly to trophoblasts cells and cause cellular injury, defective extravillous cytotrophoblast (EVT) invasion (in the decidua and spiral arteries), and induce a local inflammatory response as a result of activation of complemet\(^{8}\). Activation of complement and recruitment of inflammatory cells within the decidual tissues are necessary steps in APA-induced pregnancy loss\(^{66}\).

The negative effect of APS on pregnancy is most likely tied to abnormal placental function\(^{2}\). Adverse pregnancy outcomes in women with APS may result from poor placental perfusion.
due to localised thrombosis, perhaps through interference by APA antibodies with trophoblastic annexin V\(^{(30)}\).

Some investigators have found narrowing of spiral arteries, intimal thickening, acute atherosclerosis and fibrinoid necrosis in the placenta of women with fetal loss associated with APS. Others have found extensive placental necrosis, infarctions and thrombosis\(^{(2)}\). APAs may activate endothelial cells as indicated by increased expression of adhesion molecules, secretion of cytokines, and production of arachidonic acid metabolites\(^{(2)}\).

The pathogenesis of APA-mediated thrombosis probably involves several pathogenic mechanisms including thrombogenic microparticles derived from maternal endothelial cells, platelets and trophoblasts\(^{(67)}\). Other mechanisms are inhibition of the natural antithrombotic proteins, such as protein C, TF pathway inhibitor, annexin V, activation of the complement system and impairment of fibrinolysis which regulate thrombus remodelling and dissolution\(^{(68)}\).

Vitamin D is essential for calcium and bone mineralism, but is also a mediator of many other effects such as modulation of the immune response, being able to combat certain microorganisms\(^{(69)}\). Vitamin D deficiency has been reported to be common among patients with APS and is associated with clinically defined thrombotic events. Vitamin D deficiency (serum level \(\leq 15\) ng/ml) occurred in 50% of cases with APS compared to 30% of control subjects significantly correlating with thrombosis, neurological and ophthalmic manifestations, pulmonary hypertension, \textit{livedo reticularis} (a vascular condition characterized by purplish mottling of the skin) and skin ulcers\(^{(69)}\). An inverse correlation between vitamin D levels and thrombosis was found in this cohort\(^{(69)}\). Vitamin D is a potent inhibitor of the anti-\(\beta2\)GPI antibody-mediated expression of TF induced by endothelial cells\(^{(69)}\). Thus, vitamin D deficiency might be associated with decreased inhibition of TF expression and increased coagulation in APS.

Studies have also shown that inflammatory mechanisms in the placental bed may contribute to APS\(^{(64)}\). Some studies suggest that APA induce a pro-coagulant response in endothelial cells and monocytes through interaction with toll-like receptor-4 (TLR-4)\(^{(64)}\).

**11. Therapeutic options**

Over a long period treatment of APS included low-dose aspirin either alone or combined with prednisone, unfractioned heparin or low molecular weight heparin (LMWH), intravenous immunoglobulin infusion or plasma exchange\(^{(36)}\). Warfarin crosses the placenta and is teratogenic in the first trimester\(^{(8)}\). Women, who are on long-term warfarin treatment because of previous thrombosis, should switch to heparin when trying to conceive or when pregnancy is confirmed\(^{(8)}\). In high risk groups, such as women with mechanical heart valves, warfarin may be used in pregnancy, but only after organogenesis (6th-12th week) because of high risk of fetal malformations\(^{(8)}\). Warfarin treatment is however, also associated with spontaneous abortions, prematurity and CNS abnormalities\(^{(70)}\). As warfarin cross the placenta and subsequently affect fetal coagulation, there is a risk for bleeding complications in the fetus and during birth\(^{(71)}\). In the Cochrane review by Empson \textit{et al.} it was concluded that a combination therapy with heparin and aspirin may reduce pregnancy loss in women with APA by 54%\(^{(36)}\). Heparin combined with aspirin reduced the pregnancy loss more than
aspirin alone (relative risk (RR) 0.46; 95% CI 0.29-0.71) \(^{(36)}\). In the trials of prednisone and aspirin, no benefit was shown, rather a significant increase in prematurity (RR 4.83; 95% CI 2.85-8.21) \(^{(36)}\). In addition, prednisone was also associated with a 3.5-fold (95% CI 1.5-8.2) greater risk of gestational diabetes than aspirin alone, heparin and aspirin, or placebo \(^{(72-74)}\). Prednisone appears to have no role in the treatment of recurrent pregnancy loss associated with APA antibodies \(^{(36)}\).

Current management of APS in pregnancy generally includes heparin combined with aspirin. LMWHs are at least as effective as unfractioned heparin and are safer \(^{(21,71)}\). The rationale of this combination is that aspirin may inhibit APA mediated hypercoagulopathy in the intervillous space of the placenta while heparin may prevent APA from interfering with cytotrophoblast migration and promote blastocyst implantation in addition to prevention of venous thrombosis \(^{(75)}\).

Prolonged heparin treatment may induce osteoporosis. Recently, there has been a move towards low molecular weight heparin because of the advantages of daily dosing and a perception that it may have less effect on bone mineral density than heparin \(^{(36)}\).

The pregnancy-associated prothrombotic changes in the coagulation system are maximal immediately after delivery \(^{(21)}\). Despite lack of controlled studies regarding duration of anticoagulation, it is well accepted that persistent APA-positive women require post-partum anticoagulation. Therefore, it is desirable to continue LMWH during labor or delivery in women receiving antenatal thromboprophylaxis \(^{(21)}\). The duration of recommendations range from 3-5 days \(^{(21)}\), to 6-8 weeks \(^{(76)}\) and up to 12 weeks \(^{(77)}\).

### 12. Use of anticoagulants in lactating women

Heparin and LMVHs are not secreted into breast milk and can be safely given to nursing mothers. Warfarin is safe after delivery and for breast feeding, although it requires close monitoring, frequent visits to an anticoagulant clinic and carries an increased risk of postpartum hemorrhage and perineal hematoma compared with LMWH \(^{(21)}\). Warfarin does not induce an anticoagulant effect in the breast-fed infant. Therefore, the use of warfarin in women who require postpartum anticoagulation therapy is safe and these women should be encouraged to breast feed \(^{(78)}\).

No randomised controlled trials have investigated prevention in women with a history of late miscarriage, fetal death and IUGR. Most obstetricians would consider treatment with low-dose aspirin and prophylactic dose of (low molecular weight) heparin in such cases. In women with APA antibodies, and a history of severe preeclampsia, at least low dose aspirin (75-80 mg once a day) is recommended \(^{(79)}\). Glucorticoids, cytotoxic agents, and intravenous immunoglobulin have no confirmed benefit and should not be used to treat pregnant women with APS \(^{(79)}\).

### 13. Contraception after birth

Oral estrogen coating contraceptives increase the maternal thrombotic risk of women with APAs and SLE \(^{(80)}\). Therefore, intrauterine devices are probably more appropriate. However, progesterone-only contraceptives do not increase the risk of thrombosis \(^{(81)}\). If a woman with
APS wants to be pregnant again, pre-conceptional treatment deserves consideration\(^2\). Some women with APS may need life-long warfarin treatment.

14. References


The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. From that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities. This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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