A brief history of antiphospholipid antibodies and antiphospholipid syndrome

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ABSTRACT

AIMS: To review the historical reports on antiphospholipid antibodies (aPL) from the early years of the 20th century; to outline the cardinal features of the antiphospholipid syndrome (APS) from 1983 on, including clinical criteria, etiopathogenesis and current therapy.

METHODS: Literature review using PubMed. Articles on the history of aPL and APS were selected.

RESULTS: The original aPL were described in patients with syphilis yet in 1906 by Wassermann. A first definition of lupus anticoagulant was proposed in 1963, while the anticardiolipin antibody (aCL) test was depicted twenty years later. The APS, initially reported by Hughes in 1985 as the “aCL syndrome”, is one of the most prevalent acquired thrombophilia. Venous and arterial thrombosis, associated or not to pregnancy morbidity, comprise the main features. It is a novel disorder firstly associated to systemic lupus erythematosus. A primary form of APS was put forward in 1989, and many APS variants are currently known. Lifelong, full-dose anticoagulation is the mainstream for treatment of thrombotic APS. In obstetric APS, the combination of acetil-salicilic acid and enoxoparin has been a mostly effective therapy.

CONCLUSIONS: The sequential characterization of aPL since Wassermann in 1906, and later of the APS in the 1980-thies, is a rather interesting example of how a new entity is sketched step by step. APS is an intriguing novel cause of autoimmune thrombophilia, with a complex pathogenesis and a plethora of clinical and laboratory abnormalities. Treatment is based on life-long anticoagulation.

KEYWORDS: anti-phospholipid antibody syndrome; antiphospholipid syndrome; Hughes syndrome; thrombosis; pregnancy complication.
INTRODUCTION

The antiphospholipid syndrome (APS) is one of the few autoimmune disorders of recent description. APS is a complex thrombotic diathesis of young people, and one of the most prevalent acquired thrombophilia in clinical medicine. The condition is marked by recurrent venous and arterial thrombosis, pregnancy morbidity and presence of antiphospholipid antibodies (aPL) [1]. APS is a typical model of multiorganic and multifaceted thrombophilia. Its management involves a large range of medical specialties, including, among others, Rheumatology, Immunology, Neurology, Nephrology, Vascular Surgery and Obstetrics.

As noted throughout this paper, the terminology APS is rather misleading: the main antigens are not themselves phospholipid, but rather phospholipid cofactors; one of the aPL is named lupus anticoagulant (LA), but APS occurs independently of systemic lupus erythematosus (SLE). Lastly, aPL prolong the clotting time, but in vivo they are associated with thrombosis [2].

In this article, we will approach the chronological history of aPL and APS, from the early reports on aPL in the beginning of the 20th century to the original APS description by Hughes and Harris in the 1980s. We will also address the APS criteria and the several APS variants described from then on. The etiopathogenesis and the current therapeutic trends will be objectively reviewed.

ANTIPHOSPHOLIPID ANTIBODIES: THE HISTORY

In 1906, Wassermann et al. [3] described the first assay using a phospholipid substrate (bovine cardiolipin). This complement-fixation test was the original nontreponemal test to diagnose syphilis. In 1932, Eagle [4] stated that the syphilitic antibody described by Wassermann recognized a lipoid emulsion containing cardiolipin and auxiliary lipids.

Nowadays, it is well known that the "Wassermann serum" reacts to cardiolipin in the presence of cholesterol and phosphatidylcholine [5]. Over the time, and considering the problem of false-positivity in autoimmune diseases, the Wassermann reaction was replaced by methods such as the Venereal Disease Research Laboratory (VDRL) test and treponemal immune assays. The interface of false-positivity for syphilis and autoimmune disorders, namely SLE and APS, still affords an interesting debate. VDRL preparation includes cardiolipin, phosphatidylcholine and cholesterol [6], a more purified lipoid emulsion bound by the Wasserman antibody. As a nontreponemal microfloculation assay, VDRL, was firstly developed in the eponymous laboratory and fully described yet in 1946 [7]. The test works as a practical and rapid screening for syphilis and can be used to monitor treatment.

In a very important study coordinated by Harris et al. [8] in 1988, the specificities of syphilitic and autoimmune sera were clarified. While the syphilis antibody, usually an immunoglobulin (Ig) M binds strongly to cardiolipin in the presence of phosphatidylcholine and cholesterol, sera from patients with APS/SLE bind weakly to cardiolipin within the VDRL [8]. This provides an interesting explanation for the false-positive results of VDRL (titer 1/16 or less) in the diagnosis of syphilis, due to autoimmune conditions. More recently, it has been demonstrated that anti-Treponema pallidum antibodies react to cardiolipin and VDRL independently of the presence of beta2-glycoprotein 1 (beta2-gp1), an antigenic phospholipid cofactor. Differently, antocardiolipin antibodies (aCL) of APS/SLE patients are clearly beta2-gp1-dependent in solid assays [9].

Taking these data altogether [3-9], we can figure that the history of aPL is strongly linked to the history of syphils tests. Nowadays, when we evaluate a patient whose differential diagnosis includes syphilis and SLE/APS, the correct interpretation of these assays can make the difference. Moreover, a low VDRL in the absence of a positive treponemal test must call the attention for the presence of a circulating aPL.

The second aPL we would like to focus is the so-called LA. This aPL binds to phospholipids and phospholipid cofactors in coagulation assays, prolonging particularly the activated partial thromboplastin time (APTT) and the Russel viper venom time (RVVT). In general terms, confirmation of presence of LA is based in three steps: prolongation of APTT and/or RVVT; no correction of clotting times with mixing studies using normal plasma; correction of clotting times with a phospholipid source. LA is a misnomer, since it paradoxically predisposes to thrombosis.

Abbreviations: aPL, antiphospholipid antibodies; aCL, anti-cardiolipin antibodies; APS, antiphospholipid syndrome; APTT, activated partial thromboplastin time; ASA, acetyl salicylic acid; CAPS, catastrophic APS; ELISA, Enzyme-Linked Immunosorbent Assay; GPL, IgG phospholipid antigens; Ig, immunoglobulin; LA, lupus anticoagulant; MPL, IgM phospholipid antigens; RVVT, Russel viper venom time; SLE, systemic lupus erythematosus; VDRL, Venereal Disease Research Laboratory.

by interacting \textit{in vivo} with phospholipids and/or beta2-gpI of platelet membranes [10].

Of note, the original description of a "lupus inhibitor" by Conley [11] dates from 1952 in a SLE patient with a hemorrhagic condition. A similar clinical picture was reported in 1963 [12]. Also in 1963, Bowie et al. [13] utilized for the first time the name LA in a case of SLE and thrombotic diathesis. This intriguing finding was confirmed by Johansson and Lassus [14] in 1974, whereby the presence of LA and thrombosis was accompanied by a false-positive VDRL. One year later, Nilsson et al. [15] firstly reported a link of LA with intrauterine fetal death.

The issue's interest increased in the beginning of the 1980s, in particular by the group of the Hammersmith Hospital in London (led by Graham Hughes). In 1983, Hughes [16] published an influential study associating the LA with cerebral disease, thrombosis and recurrent miscarriages. Also in 1983, the same group of authors reported a case series of SLE patients with LA, thrombosis, abortions and/or thrombocytopenia [17]. These reports [16, 17] embodied a future concept of an APS, ongoing at that moment.

Considering the presence of cardiolipin in the VDRL, and the previous notion that the LA bound to membrane phospholipids, a search for aPL in other platforms was a question of time. Indeed, a great advance came through with the description of the aCL radioimmunoassay by Harris et al. [18], in an historical piece of work published in The Lancet in 1983. In 1984, the first international symposium on aPL was held at the Hammersmith Hospital. In 1985, Hughes [19] summarized the clinical and laboratory data of an "aCL syndrome".

In 1987, Gharavi et al. [20] described the aCL test now in an Enzyme-Linked Immunosorbent Assay (ELISA). The IgG isotype was the most associated to thrombotic complications. According to their findings, aCL clearly cross-reacted with other negatively charged phospholipids, here including phosphatidylycerine and phosphatidic acid [20].

In 1987, with the Hughes group already settled at St'Thomas Hospital, the results of a workshop which standardized the IgG and IgM aCL assay were presented in a second aPL symposium. From then on, the aCL levels were reported in IgG phospholipid antigens (GPL) and IgM phospholipid antigens (MPL) units, being these standards widely accepted nowadays.

Yet in 1987, Harris [21] suggested the name APS instead of aCL syndrome, given the different aPL involved in thrombotic events. In an editorial entitled "syndrome of black swan" published in the British Journal of Rheumatology, he proposed a seminal set of APS criteria: venous or arterial thrombosis, recurrent fetal loss and thrombocytopenia plus presence of LA or aCL for at least two occasions eight weeks apart [21].

In 1987, during our fellowship at St'Thomas in London, we worked, orientated by Nigel Harris, with the hypothesis that LA and aCL specificities did not always overlap. In fact, we disclosed quite a number of patients with discrepant results. A case of thrombotic diathesis whereby a LA was accompanied not by aCL but yet by an antibody to phosphatidylethanolamine, a neutral phospholipid, was published in the same year [22]. Under a clinical point of view, it became clear that not all patients with APS presented SLE in parallel. Accordingly, in 1989 Asherson et al. [23] described a primary form of APS.

From 1990 ahead, the aCL method was gradually improved. Interestingly, some group of authors noticed that the use of fetal calf serum or adult bovine serum consistently augmented the binding of aCL in an ELISA. Later, it was proved that this binding was enhanced by beta2-gpI, a phospholipid cofactor present in such diluents. These findings were thereafter confirmed by the group of Krilis et al. [24], who in 1998 established the role of beta2-gpI as an important target for aPL in patients with APS. Considering the overwhelming evidence of association of aPL with a thrombotic state of young people, a more precise definition of APS criteria would be the step forward.

**THE ANTIPHOSPHOLIPID SYNDROME**

In 1999, the "aPL community" organized a workshop in Sapporo, Japan, to define criteria for APS. The so-called Sapporo criteria included arterial/venous thrombosis, pregnancy loss and presence of LA and/or aCL [25]. A more precise classification of APS was sought in 2006, at a workshop in Sydney, Australia. The Sydney criteria embraced the presence of anti-beta2-gpI antibodies [26]. These classification criteria for APS, accepted to date, is shown in **Chart 1**.

Venous obstructions predominate in lower limbs, and pulmonary embolism is a frequent complication. Thrombosis of hepatic veins, portal system, kidney and venous sinuses have all been reported, among other areas. Arterial thrombosis preponderates in brain, kidney and lower limbs, but a number of other sites can be affected. Medium and large vessels are particular compromised in this context, even though this is not absolute [25, 26]. A particular form of severe APS involving small-vessel (catastrophic APS) will be discussed ahead.
Obstetric abnormalities include abortions, fetal loss and premature birth due to preeclampsia, eclampsia or placental insufficiency [25, 26]. In 2010, a meta-analysis carried out by our group confirmed a risk association of aCL with preeclampsia [27].

Worthy of note, some patients with APS present purely obstetric morbidity. Obstetric APS can be considered a particular form of APS, according to a recent proposal [28]. A different pathogenesis is accepted for this obstetric context (see pathogenesis).

Epidemiology

Important to say, 1-5% of the healthy population have circulating aPL, mostly aCL in low levels. Thus, presence of aPL does not mean APS in strict terms. Besides immune dysregulation, genetic and environmental factors are needed to deflagrate the disease [29]. APS is one of the main causes, if not the main, of acquired thrombophilia. Its prevalence is 40-50 cases/100,000 individuals. The disease usually affects young adults, with a clear-cut predominance in females. It is estimated that 13% of cases of cerebral ischemia and 9% of cases of deep vein thrombosis are due to APS [30].

According to the Europhospholipid Registry (including approximately 1,000 patients), the primary form of APS predominates (53.1%). Secondary APS (generally concomitant to SLE) was detected in 36.1% of patients, and APS variants in the remaining [31].

Etiology and pathogenesis

Concerning to genetic factors, primary APS has been associated with presence of human histocompatibility antigens of type DR4 and DRw53. Prothrombin gen and Leiden mutations have been also described in APS patients [32].

A polymorphism of the valine/leucine system was reported in the beta2-gpl molecule, contributing to antigenicity of this phospholipid cofactor [33]. In a 2006 report, we demonstrated that IgA anti-beta2-gpl antibodies of APS patients preferentially target the domain 1 of beta2-gpl molecule, while patients with atherosclerotic disease bind domain 4 [34].

Genetic determinants per se are yet insufficient to deflagrate APS. Environmental triggers (called "second hit") are usually required to promote the appearance of clinical disease. Trauma, infection and drugs are well-recognized environmental factors associated to APS. In a genetically predisposed individual, exposure to infectious agents may give rise to aPL and APS by molecular mimicry. In animal models, passive transfer and active immunization with cardiolipin or beta2-gpl yielded thrombotic disease, suggesting a pathogenic role for aPL [35]. As to hormone factors, mice exposed to estrogen produced high levels of aCL [36].

As far as pathogenesis is concerned, aPL knowingly promote activation of platelets and endothelial cells by binding to membrane phospholipids and beta2-gpl. Activated platelets release thromboxane, a well-known vasoconstrictor. Annexin A2, an endothelial cell receptor for plasminogen and tissue plasminogen activator, has been considered a potential target for aPL. At the same time, aPL inhibit the fibrinolytic pathway and activate the complement system. The final result is intravascular thrombosis and inflammation [37].

Current concept of APS as a thrombotic and inflammatory disorder very much relies on the role of macrophages; aPL bind to macrophage "toll-like receptors", inducing release of tissue factor (responsible for setting off the coagulation cascade) and proinflammatory cytokines [38]. Among the latter, tumor necrosis factor-alfa [38] and interferon [39] are involved, so amplifying the immune response.

A pathogenetic role for complement activation is nowadays well-established in the APS [40]. The triggering of complement classical pathway at the

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Chart 1. Classification criteria for diagnosis of antiphospholipid syndrome. Diagnosis is confirmed with the presence of at least one clinical and one laboratory criteria. Antiphospholipid antibodies must be present for at least two occasions at least 12 weeks apart (Sydney criteria, ref. 26).

<table>
<thead>
<tr>
<th>Arterial or venous thrombosis, or small-vessel occlusions.</th>
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<td>Pregnancy morbidity: more than 3 unexplained losses before 10 weeks with embryo morphologically normal; at least one fetal loss after 10 weeks with normal fetus morphology; at least one premature birth of a morphologically normal fetus due to preeclampsia, eclampsia or placental insufficiency.</td>
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<td>Lupus anticoagulant: prolongation of activated partial thromboplastin time/Russel viper venom time and confirmatory mixing tests.</td>
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<td>Anticardiolipin antibodies: moderate/high levels of IgG and IgM antibodies (starting from 40 GPL and MPL, respectively).</td>
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<td>Anti-beta2-gpl antibodies: present when titer above the 99th percentile for IgG and IgM.</td>
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trophoblast surface is an important mechanism by which aPL elicit early pregnancy losses [41]. In 2013, our group originally reported a decrease of circulating CD4+CD25+Foxp3+ regulatory T cells in patients with primary APS [42]. Soon later, the finding was confirmed in patients with APS secondary to SLE [43].

**Differential diagnosis**

A broad range of clinical conditions, either hereditary or acquired, can mimic an APS. For instance, individuals with inherited thrombophilia (mostly Leiden factor, prothrombin gene and methylenetetrahydrofolate reductase mutations) can show a thrombotic diathesis early in life. All these mutations are predominantly associated to venous thrombosis; occasionally, they relate to recurrent miscarriages as well [26, 30, 44].

When a diagnosis of APS is a possibility, other acquired entities have to be ruled out. Usage of estrogen-containing oral contraceptives, cancer, trauma, postsurgery, immobilization, HIV infection and travel are frequent causes of thrombophilia in the everyday clinical practice. Except for HIV infection, venous thrombosis preponderates. Although less common, syphilis, nephrotic syndrome, systemic vasculitis, hyperhomocysteinemia, thrombotic thrombocytopenic purpura and paroxysmal nocturnal hemoglobinuria also enter the differential diagnosis of recurrent thrombosis. Pseudovasculitis such as cholesterol embolization syndrome, infectious endocarditis, Burger disease, livedoid vasculopathy and cocaine intoxication can eventually resemble an APS [26, 30, 44].

**Antiphospholipid variants**

In 2006, Asherson [45] described with great details a group of patients with devastating APS. This severe, multiorganic form of primary APS was named "catastrophic APS" (CAPS), currently named Asherson syndrome. CAPS represents not more than 1% of APS cases overall. It manifests by a small vessel vasculopathy following a trigger (trauma, infection, tumor, post-delivery). At least three organs must be involved in a week period of time. Mortality is very high [45]. Up to 2012, more than 400 cases had been reported to the CAPS registry [46].

A number of other aPL-related entities can now be considered as APS variants. A microangiopathic form of APS was proposed in 2006 for patients with small vessel vasculopathy, thrombocytopenia and microangiopathic anemia [47]. HELLP syndrome, whose hallmarks are microangiopathic hemolysis, elevated liver enzymes and low platelet count, is an intriguing disorder of late pregnancy or post-partum. Disseminated intravascular coagulation is not a rare drawback [48]. Evans syndrome, in turn, is a non-thrombotic variant of APS with immune thrombocytopenia and Coombs-positive hemolysis [49].

In 1965, the British physician Ian Bruce Sneddon described a syndrome of recurrent strokes and extensive livedo reticularis in six patients [50]. The so-called Sneddon syndrome is currently considered as an aPL-associated condition, once 40-60% of patients present some type of aPL. Hypertension and coronary disease are seen at times [51].

Some patients with features of multiple sclerosis or transverse myelitis display lupus-like disease, aPL and eventually thrombosis; the term "lupoid sclerosis" has been applied to classify these cases [52]. In 2015, we reported a case focusing the interface of cocaine abuse, retiform purpura and aPL [53].

**Treatment of antiphospholipid syndrome**

For didatic and practical reasons, treatment of APS will be here divided in thrombotic and obstetric subtypes. Primary thromboprophilaxy with low-dose acetyl-salicilic acid (ASA) should be administrated to asymptomatic individuals (or SLE patients) with persistent LA or moderate/high levels of aCL and/or anti-beta2-gpl antibodies [54].

Secondary therapy of thrombotic APS is largely based in anticoagulation. In the acute phase of thrombotic episode, standard therapy with full-dose heparin or enoxaparin is the mainstream. Following the acute phase, patients must be treated with warfarin. Anticoagulation must be lifelong, once the risk of thrombotic recurrence is high [55]. The target international normalized ratio should be 2-3 for patients with first venous events, and 3 for patients with recurrent venous events or arterial thrombosis [56]. A corrective approach of parallel thrombotic risk factors is strongly indicated [54-56].

These recommendations [54-56] are well-based on controlled trials and observational studies. Nevertheless, there are some zones of uncertainty in the treatment of particular subsets of APS. For instance, patients with clear-cut features of APS but negative for aPL ("seronegative APS"); patients with incomplete criteria for APS; patients with APS variants where thrombosis is not confirmed; and non-thrombotic forms of APS. The eventual withdrawal of
anticoagulation for patients who become aPL-negative is also a matter of controversy [57].

For patients with refractory thrombotic APS, the adding of ASA to warfarin or the use of full-dose enoxaparin replacing warfarin comprise options. The concomitant usage of warfarin and hydroxychloroquine and/or statins have been advocated in recalcitrant cases. B-cell depletion with rituximab can be utilized in severe cases of recurrent thrombosis, or in microangiopathic APS [58]. For patients with CAPS (whose mortality is 30%), a combination of intravenous heparin, corticosteroids, intravenous immunoglobulin and plasmapheresis is highly recommended [59]. Potential immunomodulatory approaches for the future might include tissue factor inhibition, P38 mitogen-activated protein kinase inhibition, nuclear factor-kappa B inhibition, newer antiplatelet drugs and complement inhibition [60].

The therapy of pregnant women with aPL or obstetric APS demands some considerations in particular. In a first pregnancy featuring LA or moderate/high levels of aCL or anti-beta2-gpI should, a primary thromboprophylaxis with ASA should be indicated. Women with previous miscarriages, fetal loss or preeclampsia are preferentially treated with the combination of ASA and low-dose enoxaparin (20-60 mg, usually 40 mg) [61]. In turn, pregnant women with previous thrombotic APS shall receive full-dose enoxaparin during the pregnancy, but this is a matter of great debate considering the risk of bleeding [62].

For "pure" obstetric APS, combined heparin and ASA reduce pregnancy loss by 54%, according to Cochrane data yet from 2005 [63]. Use of enoxaparin should be extended to the post-partum period (20-30 days) to prevent perinatal thrombosis or HELLP syndrome [64]. Despite of therapy with enoxaparin and ASA, 30% of women still develop some kind of pregnancy morbidity. Age above 30 years, previous early delivery and "triple positivity" for aPL are predictors of a complicate outcome. Treatment of refractory obstetric APS may encompass low-dose prednisone, hydroxychloroquine, pravastatin and intravenous immunoglobulin, but controlled studies are lacking [65].

**HISTORICAL SUMMARY**

APS is now named Hughes syndrome [66] in a tribute to his early clinical descriptions in the 1980s. A number of reports herein commented brought new lights in the understanding of biological role of aPL in patients with APS. Some of them had a bombastic impact in clinical practice. In **Chart 2** we cite, in chronological order, fifteen key manuscripts which modified the history of aPL/APS, selected in a strictly personal view.

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**Chart 2. Fifteen cardinal reports on the history of antiphospholipid antibodies and antiphospholipid syndrome in chronological order.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
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<tbody>
<tr>
<td>Wasserman A et al., 1906 (ref. 3):</td>
<td>report of a nontreponemal assay using phospholipid</td>
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<tr>
<td>Harris A et al., 1946 (ref. 7):</td>
<td>description of VDRL using cardiolipin as phospholipid</td>
</tr>
<tr>
<td>Conley C et al., 1952 (ref. 11):</td>
<td>description of a circulating “lupus Inhibitor”</td>
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<tr>
<td>Bowie EJ et al., 1963 (ref. 13):</td>
<td>description of the LA</td>
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<tr>
<td>Hughes GR, 1983 (ref. 16):</td>
<td>description of a “LA syndrome” featuring thrombosis</td>
</tr>
<tr>
<td>Harris EN et al., 1983 (ref. 18):</td>
<td>description of a radioimmunoassay to detect aCL</td>
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<tr>
<td>Hughes GR et al., 1985 (ref. 19):</td>
<td>description of the “aCL syndrome”</td>
</tr>
<tr>
<td>Harris EN et al., 1987 (ref. 21):</td>
<td>description of “syndrome of black swan” featuring LA/aCL</td>
</tr>
<tr>
<td>Harris EN et al., 1988 (ref. 8):</td>
<td>description of specificities of aCL and antibodies to VDRL</td>
</tr>
<tr>
<td>Asherson RA et al., 1989 (ref. 23):</td>
<td>proposition of a primary form of APS</td>
</tr>
<tr>
<td>Hunt JÈ et al., 1992 (ref. 9):</td>
<td>definition of aCL specificities in APS versus infections</td>
</tr>
<tr>
<td>Sheng Y et al., 1998 (ref. 24):</td>
<td>description of beta2-gpI as an important target for aPL</td>
</tr>
<tr>
<td>MiyakisS et al., 2006 (ref. 26):</td>
<td>definition of current Sidney criteria for diagnosis of APS</td>
</tr>
<tr>
<td>Asherson RA, 2006 (ref. 45):</td>
<td>description of “catastrophic APS”</td>
</tr>
<tr>
<td>D’ippolito S et al., 2014 (ref 28):</td>
<td>proposition of obstetric APS as a sole entity</td>
</tr>
</tbody>
</table>

VDRL, Venereal Disease Research Laboratory; aCL, anticardiolipin antibodies; LA, lupus anticoagulant; APS, antiphospholipid syndrome; beta2-gpI, beta2-glycoprotein I; aPL, antiphospholipid antibodies.
CONCLUSIONS

The history of aPL is robustly connected to the original nontreponemal syphilis assays. APS is a novel disorder fully described in the last two decades of 20th century. Arterial and/or venous thrombosis and pregnancy morbidity are hallmarks of APS, and three sets of aPL (LA, aCL, anti-beta2-gpI antibodies) are of clinical importance. The mechanisms by which aPL link up to thrombosis are complex, involving fundamentally activation of platelets, endothelial cells and macrophages.

APS is one of the most frequent causes of acquired thrombophilia in young adults. Anticoagulation should be continuous for patients with the thrombotic form of APS. The combination of ASA and enoxaparin is a standard therapy for obstetric morbidity. A great deal of research in pathogenesis, clinical aspects and therapy has turned APS a mostly fascinating condition in modern Internal Medicine.

NOTES

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Authors’ contributions
The authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results
The authors declare to have had full access to the available data and they assume full responsibility for the integrity of this review.

REFERENCES


