Non-criteria manifestations of antiphospholipid syndrome: An overview

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Abstract

While the classification criteria for definite antiphospholipid syndrome (APS) include specific thrombotic and obstetric manifestation, there are numerous clinical features also present in patients with antiphospholipid antibodies (aPL), which are not included in the classification criteria. The term “non-criteria” is currently used to refer to these manifestations. This review intends to provide a summarized, but far-reaching description, of the non-criteria manifestations present in the literature, with special focus on their association with APS and potential impact on the disease course. We analyze the following involvements: cardiac (cardiac microvascular disease and valvular heart disease), dermatological (*livedo reticularis/racemosa*, livedoid vasculopathy and skin ulcers), ear, nose, and throat (sensorineural hearing loss), endocrinological (adrenal insufficiency due to hemorrhagic infarction), hematological (hemolytic anemia and thrombocytopenia), musculoskeletal (ischemic bone necrosis), neurological (acute ischemic encephalopathy, chorea, cognitive dysfunction, epilepsy/seizures, migraine, and transverse myelitis), pulmonary (diffuse alveolar hemorrhage and pulmonary hypertension), ophthalmologic (*amaurosis fugax*), renal (APS nephropathy), vascular (superficial vein thrombosis), and obstetric (infertility, *in vitro* fertilization failure, and placenta-mediated complications) manifestations. Although gaining relevance in the current practice, the exact level of association of the different non-criteria manifestations with APS/aPL is still unclear or scarcely characterized in most cases.

Key words: Antiphospholipid syndrome. Antiphospholipid antibodies. Non-criteria manifestations.

Introduction

The 2006 classification criteria for definite antiphospholipid syndrome (APS) include specific manifestations – either thrombotic (arterial, venous, or small-vessel) or obstetric¹. However, there are several additional manifestations that are also present in patients with antiphospholipid antibodies (aPL), but not included in the classification criteria. The term “non-criteria” manifestations has been gradually and informally adopted throughout the literature to refer to these

clinical features, and a rising number of publications discuss their relevance^{2,3}. The 2014 report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* suggested the inclusion of some manifestations as part of APS criteria revision². In the initiative for *Development of New International APS Classification Criteria*, currently underway, many of these non-criteria manifestation are analyzed as candidate criteria⁴. A recent article approaches the treatment of some of these manifestations, namely

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cardiac, pulmonary, hematologic, cutaneous, and neurological involvements⁵.

In this review, we intend to cover, in a summarized but far-reaching manner, the existing “non-criteria” manifestations described in the literature (Table 1), focusing on the strength of their association with aPL and their potential impact on the disease course, and allowing for a general view of this subject.

Cardiac manifestations

Cardiac microvascular disease

There are case reports of APS patients with diffuse cardiomyopathy or evidence of myocardial ischemia with normal coronaries, indicating microvascular disease as a plausible mechanism^{6,7}. Histology of these patients may reveal occlusive microthrombosis of small myocardial arterioles and areas of micro-infarction surrounding the affected arterioles, with consequential myocardial necrosis⁶. This situation occurs both in classic and catastrophic APS patients⁸. The absence of vasculitis changes in these patients supports the hypothesis that aPL exert a direct thrombotic effect^{6,9}. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including cardiac microvascular disease) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Valvular heart disease

Valvular disease in APS occurs in the form of valve lesions (thickening or vegetations) and/or valve dysfunction in the absence of rheumatic fever or infective endocarditis⁶. Valve lesions are defined as (i) valve thickness > 3 mm; (ii) localized thickening involving the proximal or middle portion of the leaflets; or (iii) irregular nodules on the atrial face of the mitral valve and/or the vascular face of the aortic valve². The reported frequency in primary APS ranges from 10% to more than 60%¹⁰. Histopathological findings may include fibrosis, calcification, vascular proliferation, verrucous thrombosis on endocardial valvular surfaces, and thrombosis of intravalvular capillaries⁶. Possible pathogenic mechanisms for these lesions in aPL patients include both thrombotic and inflammatory mechanisms, such as deposition of aPL and complement components or the deposition of fibrin platelet thrombi on the affected valve¹⁰. Although the role of aPL in heart lesions has not been categorically proven, most studies

Table 1. Non-criteria manifestations of the antiphospholipid syndrome

Affected organ/system	Non-criteria manifestation
Cardiac	Cardiac microvascular disease Valvular heart disease
Dermatological	<i>Livedo reticularis/racemosa</i> Livedoid vasculopathy Skin ulcers Splinter hemorrhages
Ear, nose, and throat	Sensorineural hearing loss
Endocrinological	Adrenal insufficiency due to hemorrhagic infarction
Hematological	Evans syndrome Hemolytic anemia Positive Coombs' test Thrombocytopenia
Musculoskeletal	Ischemic bone necrosis
Neurological	Acute ischemic encephalopathy Brain MRI white matter lesions Chorea Cognitive dysfunction Epilepsy/seizures Migraine Pseudo-multiple sclerosis Transverse myelitis
Pulmonary	Diffuse alveolar hemorrhage Pulmonary hypertension
Ophthalmological	<i>Amaurosis fugax</i>
Renal	APS nephropathy
Vascular	Superficial vein thrombosis Raynaud's phenomenon
Obstetric	Infertility Late intrauterine growth restriction (after 34 weeks) Late pre-eclampsia (after 34 weeks) <i>Abruptio placentae</i> Placental hematoma Preterm birth (> 34-< 37 weeks) Puerperal pre-eclampsia Two or more unexplained IVF failures Two unexplained spontaneous abortion < 10 weeks

APS: antiphospholipid syndrome; IVF: *in vitro* fertilization; MRI: magnetic resonance imaging.

evaluated in two systematic reviews display an association between the presence of aPL and valvular lesions^{11,12}. The risk of valvular heart disease was highest for lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) of the IgG isotype¹². The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding valvular heart disease as of “moderate”

quality, issuing a “strong recommendation” for this manifestation to be included as part of the APS criteria revision². In the *Phase III of the Development of New International Classification Criteria for APS*, heart valve disease occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Dermatological manifestations

Livedo reticularis/racemosa

Livedo is the most frequent dermatologic manifestations of APS (observed in 24.1% of patients of the Euro-phospholipid cohort)^{13,14}, defined as a persisting violaceous, red, or blue reticular or mottled pattern of the skin, not reversible with rewarming¹. It can consist of regular unbroken circles (*livedo reticularis*) or irregular-broken circles (*livedo racemosa*)¹⁵. Several associations have been reported with *livedo*, namely seizures, arterial events (and decreased venous events), cerebral or ocular vascular events, cognitive dysfunction, avascular necrosis, heart valve abnormalities and hypertension¹⁶⁻²⁰. The report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding *livedo reticularis* as of “moderate” quality, “recommending” its inclusion as part of the APS criteria revision². In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including *livedo racemosa*) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Livedoid vasculopathy and skin ulcers

Although livedoid vasculopathy is associated with APS, the exact prevalence is unclear¹⁵. It consists of a non-inflammatory occlusion of the small vessels of the skin due to thrombosis and deposition of fibrin in the vessel walls, mimicking vasculitis²¹. It mostly affects young women and presents as focal purpuric painful lesions that ultimately form irregularly shaped ulcers. These lesions heal slowly and leave porcelain-white, stellate, atrophic scars surrounded by telangiectasia, hemosiderin deposition, and hyperpigmentation (*atrophie blanche*)^{15,22}.

Skin ulcers in APS can occur due to various etiologies, including APS-related vasculopathy, secondary lesions in the context of prior thrombosis, or ulcerations secondary to warfarin treatment⁵.

In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including livedoid vasculopathy) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Ear, nose, and throat (ENT) manifestations

Sensorineural hearing loss

The link between autoimmune diseases and sudden sensorineural hearing loss has been described as early as the 1970s and 1980s^{23,24}, with various case reports and case series reporting this complication specifically in APS and systemic lupus erythematosus (SLE) patients²⁵⁻²⁹. Among the possible pathogenic mechanisms, microthrombosis of the cochlear vessels associated with aPL is a potential etiology³⁰. A recent review found that most of the patients with sensorineural hearing loss and APS were males, with a clinical presentation including vertigo, tinnitus, and headache, and 75% of patients presented bilateral disease³¹. In terms of aPL profile, LA and aCL were found in equal proportions³¹. Regarding treatment, all patients were anticoagulated, and aspirin was added in 25% of the cases, with a complete resolution or improvement of the symptomatology observed in 25% of the patients³¹.

Endocrinological manifestations

Adrenal insufficiency due to hemorrhagic infarction

Although rare (0.4% of APS patients)³², adrenal insufficiency is the most common endocrinologic manifestation of APS and can be its presenting symptom³³. It has also been frequently observed as part of the multiorgan failure characteristic of catastrophic APS³³. Data about this manifestation are mostly available from case reports and case series³⁴⁻³⁸. The pathogenesis is unclear, but some mechanisms are proposed: (i) rich adrenal arterial supply with a limited venous drainage predisposing patients to thrombosis, followed by hemorrhagic infarction of the adrenal glands; (ii) development of adrenal hemorrhage following surgery or anticoagulant therapy; and (iii) accumulation in the adrenal cells of late endosomes, which express epitopes recognized by aPL³³. In a review of cases reported in the literature, the most frequent treatments were steroid replacement therapy (84% of patients), followed by anticoagulation (52%) and aspirin (6%)³⁸. In the *Phase III of the Development of New International Classification*

Criteria for APS, microvascular disease (including adrenal hemorrhage) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Hematological manifestations

Hemolytic anemia

The Euro-phospholipid cohort reported the presence of autoimmune hemolytic anemia (AIHA) in 9.7% of patients¹³, while a study of 308 APS patients found a prevalence of 10.4%³⁹. This study also suggested an association between AIHA, arterial thrombosis, heart valve disease, epilepsy or chorea, and *livedo reticularis*³⁹. A potential mechanism for AIHA in APS is cross-reactivity between aPL and red cell membrane phospholipids⁴⁰. A recent systematic review and meta-analysis attempting to clarify the relationship between aPL and AIHA found the highest prevalence of AIHA in SLE patients with APS/aPL, low/moderate prevalence in SLE patients without aPL, and a lower prevalence in primary APS⁴¹.

Thrombocytopenia

Thrombocytopenia is one of the most commonly present non-criteria manifestations, with a reported prevalence ranging from 16% to 53% in APS patients⁴². There is limited knowledge on the pathogenesis of thrombocytopenia in APS, but various mechanisms are proposed: (i) increased platelet destruction, either immune-mediated (caused by aPL or associated immune thrombocytopenic purpura), due to thrombotic microangiopathy (as in the case of catastrophic APS), or drug-induced; (ii) decreased platelet production; (iii) increased platelet pooling; and (iv) pseudothrombocytopenia⁴³. Thrombocytopenia in APS is usually described as mild ($70\text{--}120 \times 10^9$ platelets/L) and benign⁴⁴; nevertheless, in a study of 51 APS patients with thrombocytopenia, 31% received some form of specific treatment (either corticosteroids, intravenous immunoglobulin or rituximab)⁴⁵. Regarding the disease course, in this same study, the authors observed that if thrombocytopenia was not present at diagnosis, patients had only 2.6% risk to develop it during follow-up⁴⁵. Furthermore, thrombocytopenia was particularly related with a high-risk aPL profile (LA and triple positivity), but the decreased platelet count had no proven impact on the risk of major bleedings⁴⁵. A tempting idea would be the possibility of thrombocytopenia serving as a marker for

future development of SLE in APS patients, but different publications could not establish this association^{46–48}. However, a study of 138 patients with aPL positivity and thrombocytopenia (i.e., fulfilling laboratory but not clinical criteria of APS) described a 5 times higher risk of future thrombosis in these patients compared with those with normal platelet counts⁴⁹. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding thrombocytopenia as of “low” quality, but “recommended” its inclusion as part of the APS criteria revision². In the *Phase III of the Development of New International Classification Criteria for APS*, thrombocytopenia occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Musculoskeletal manifestations

Ischemic bone necrosis

There is an increased incidence of osteonecrosis in primary APS patients in the absence of other predisposing factors, suggesting an association between osteonecrosis and aPL²⁰. The reported incidence varies between 0.9% and 20% in primary APS patients^{50,51}. Regarding pathogenesis, aPL may play a role in osteonecrosis development by promoting thrombotic vasculopathy in the intraosseous microcirculation²⁰. In a prospective study of 30 primary APS patients who had never received corticosteroids, 6 (20%) had evidence of asymptomatic avascular necrosis on magnetic resonance imaging (MRI)⁵². In the same study, avascular necrosis tended to develop more frequently in younger individuals, and *livedo reticularis* was more frequent in patients with avascular necrosis²⁰.

Neurological manifestations

Acute ischemic encephalopathy

First described in association with APS in 1989⁵³, acute ischemic encephalopathy has been observed in several patients with aPL^{54–56} and it was present in 1.1% of patients of the Euro-phospholipid cohort¹³. Clinical findings include confusion, asymmetrical quadriparesis, hyperreflexia, and bilateral extensor plantar responses, with imaging exams revealing cortical hypodensities on MRI^{57,58}. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including acute ischemic encephalopathy) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Chorea

Chorea is described as a rare complication of APS, with a prevalence of 1.3% in the Euro-phospholipid cohort¹³, but constitutes the most common movement disorder associated with the disease. Though still uncertain, the pathophysiology may be related with (i) cerebral infarctions and white matter changes due to a thrombo-occlusive mechanism; or (ii) immune-mediated damage against basal ganglia epitopes⁵⁹. A study of 50 patients with APS and chorea showed a significant percentage of younger women and SLE-associated APS patients and described a possible association with the initiation of oral contraceptives^{60,61}. The report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding chorea as of “low” quality, but “recommended” its inclusion as part of the APS criteria revision².

Cognitive dysfunction

The reported frequency of cognitive dysfunction in aPL-positive patients ranges from 19% to 40%, with dementia observed in much lower percentages (0% to 6%)⁶². Cognitive dysfunction is a broad term that encompasses different manifestations, and patients may report difficulty with memory, attention, and concentration, or the dysfunction may be subclinical and apparent only with neuropsychological testing⁶³. A study of 60 APS patients found a higher frequency of cognitive impairment in comparison with matched controls, reporting also an increased risk for cognitive dysfunction in patients with *livedo reticularis* and white matter lesions on brain MRI¹⁹. Another study found cognitive dysfunction to be more common in aPL high-titer patients in comparison with moderate-titer patients¹⁹. Although it would be tempting to correlate cognitive deficits with cerebral ischemic lesions, while some studies of MRI in APS patients display high frequency of cortical, subcortical, and basal ganglia infarcts, others focusing specifically on cognition failed to demonstrate an increased numbers of infarcts in patients with APS with cognitive deficits compared with controls⁶⁰.

Epilepsy/seizures

The prevalence of epilepsy in APS is reported to range from 3% to 10%, with higher prevalence in SLE-associated APS^{5,13,64}. Although the pathogenic

mechanism is not clear, possibilities include: (i) occlusion of vessels supplying the nervous tissue and (ii) direct interaction of antibodies with phospholipids of neural cells^{65,66}. Regarding clinical presentation, temporal lobe epilepsy is particularly prominent in APS⁶⁷. The report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding seizures as of “very low” quality, recommending against its inclusion as part of the APS criteria revision².

Migraine

In the Euro-phospholipid cohort¹³, migraine featured as the most common neurologic manifestation, being present in 20.2% of patients. In the literature, the reported prevalence ranges from 0% to 30%⁶⁸. Nevertheless, the association between aPL and migraine is still not categorical, with conflicting studies regarding this matter⁶⁸. Among possible pathogenic mechanisms, platelet function abnormalities and interaction of LA with neuronal phospholipids such as sphingomyelin have been hypothesized^{68,69}. In a review by Hughes⁷⁰, the typical clinical picture is migraine (often premenstrual) starting in teenage years, with subsequent improvement and return in the 30s or 40s; additionally, a strong family history of headaches or migraine is reported, and visual or speech disturbance or transient ischemic attacks occur concurrently in some patients⁷⁰. Anticoagulation is still considered the mainstay treatment, with a resolution or improvement of the migraine standing as an additional clue to its relationship with APS^{68,71,72}. Nevertheless, the report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding migraine as of “very low” quality, recommending against its inclusion as part of the APS criteria revision².

Transverse myelitis

The prevalence of transverse myelitis in APS is estimated to be around 0.4–4%⁵⁹. Plausible pathophysiological mechanisms of transverse myelitis in patients with aPL include: (i) vasculitis; (ii) arterial thrombosis resulting in ischemic cord necrosis; and (iii) direct interaction between aPL and spinal cord phospholipids^{2,73}. Various studies additionally report an association between the presence of aPL and transverse myelitis in SLE patients^{74,75}. The report of the 14th *International Congress on aPL Technical Task Force on APS Clinical*

Features classified the evidence regarding longitudinal myelitis as of “low” quality, but “recommended” its inclusion as part of the APS criteria revision².

Pulmonary manifestations

Diffuse alveolar hemorrhage

First described in association with APS in 1991⁷⁶, diffuse alveolar hemorrhage is a rare manifestation of APS (0.7% in the Euro-phospholipid cohort together with acute respiratory distress syndrome and pulmonary artery thrombosis)¹³, but occurs in 12% of catastrophic APS patients⁷⁷. Possible mechanisms behind this complication in APS include: (i) aPL-induced pulmonary capillaritis; (ii) microvascular thrombosis generating alveoli hemorrhage; (iii) aPL activation of the mTOR kinase leading to endothelium proliferation and consequent vasculopathy; and (iv) complement activation⁷⁸. In a recent review of cases of alveolar hemorrhage associated with APS, this complication was the initial feature of APS in 11% of cases; 65% achieved remission, 55% experienced recurrent disease, and 21% died⁷⁸. Regarding treatment, it should be noted that anticoagulation has not been shown to be beneficial in preventing or treating alveolar hemorrhage in APS patients, with anticoagulation being usually transiently discontinued during the bleeding episode and later restarted depending on the patient's condition⁷⁸. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including pulmonary hemorrhage) occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Pulmonary hypertension

There is growing evidence on the association between pulmonary hypertension and the presence of aPL⁷⁹. Among SLE patients, a meta-analysis found that aPL can identify patients at risk for pulmonary hypertension⁸⁰. There are various pathogenic mechanisms proposed, including: (i) large vessel and small vessel thrombosis; (ii) pro-inflammatory effects of aPL; (iii) Libman-Sacks endocarditis and left-sided valvular disease; and (iv) chronic thromboemboli and associated endothelial remodeling^{79,81,82}. The prevalence of this manifestation in the Euro-phospholipid cohort was 2.2%¹³, while another European study of 114 APS patients displayed a prevalence of 3.5% in primary APS and 1.8% in APS associated with other autoimmune

diseases⁸³. The presence of aPL is suggested to be associated with pulmonary hypertension of across all the five WHO groups⁸¹. A review suggested that the outcome of pulmonary hypertension in aPL-positive patients seemed to be linked with the occurrence of new venous thromboembolic events or left-sided heart abnormalities⁷⁹.

Ophthalmological manifestations

Amaurosis fugax

Ocular changes can be found in 8-88% of APS patients, with manifestations occurring mainly due to thrombotic events in central retinal vessels^{84,85}. In the case of *amaurosis fugax*, if binocular, it usually represents central nervous system ischemia⁸⁶. This manifestation was present in 2.2% of patients of the Euro-phospholipid cohort¹³. In a recent study featuring a cohort of 105 primary APS patients, *amaurosis fugax* starred as the most prevalent ophthalmological involvement, being present in 30 (29%) patients, and associated with the presence of *livedo reticularis*, Raynaud's phenomenon, and aCL⁸⁷.

Renal manifestations

APS nephropathy

The first reports of APS nephropathy date back to 1990⁸⁸, with the description as a distinct clinical entity occurring in 1999. It comprises renal small vessel vasculopathy with thrombotic microangiopathy, fibrous intimal hyperplasia, arterial and arteriolar recanalizing thrombi, fibrous arterial occlusion, focal cortical atrophy, tubular thyroidization, and absence of vasculitis⁸⁹⁻⁹¹. The clinical presentation includes hypertension, acute or chronic kidney injury, proteinuria (mild to nephrotic), and hematuria^{91,92}. The prognosis is variable but includes high prevalence of chronic hypertension in most series, while proteinuria, nephrotic syndrome, chronic renal failure, or end-stage renal disease also occurs⁹¹. The report of the 14th *International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding APS nephropathy as of “moderate” quality, issuing a “strong recommendation” for it to be included as part of the APS criteria revision². In the *Phase III of the Development of New International Classification Criteria for APS*, chronic aPL-related nephropathy occurred with higher frequency in cases categorized as “highly likely” to have an APS diagnosis⁴.

Vascular manifestations

Superficial vein thrombosis

Although common in APS (11.7% of patients in the Euro-phospholipid cohort)¹³, the limited evidence regarding the correlation between superficial vein thrombosis and APS/aPL together with the intent to avoid classifying other diseases as APS (e.g., Behçet's disease, where aPL and superficial vein thrombosis can coexist) has determined a maintained exclusion from the classification criteria². Nevertheless, in a prospective cohort study of 92 patients with SLE and/or aPL with a median follow-up of 35 months, superficial vein thrombosis carried a hazard ratio of 7.45 for the occurrence of thromboembolic events, suggesting a possible prognostic significance⁹³. The report of the 14th International Congress on aPL Technical Task Force on APS Clinical Features classified the evidence regarding superficial vein thrombosis as of "low" quality, but "suggested" its inclusion as part of the APS criteria revision².

Obstetric manifestations

Infertility

The concept of a relationship between some infertility cases and APS/aPL, although tempting, is still controversial. Different pathogenic mechanisms could explain this link, namely (i) aPL interfering with oocyte development and uterine decidualization and (ii) neutrophil extracellular traps promoting coagulation⁹⁴. A recent review analyzed 16 studies assessing aPL positivity rates in infertile women and control populations, while 10 studies showed aPL elevation in women with unexplained infertility comparing with healthy controls, six showed no significant differences⁹⁴. The authors concluded that currently there is not enough evidence to support the routine testing of aPL in patients with infertility⁹⁴.

In vitro fertilization (IVF) failure

Following the same reasoning as above, aPL have been hypothesized to be related with IVF failures⁹⁵. However, this association is once again controversial. The aforementioned review also analyzed studies evaluating the relevance of aPL in women undergoing IVF. Among 33 studies, 15 showed some contribution of aPL to IVF failure, while 18 failed to show this association⁹⁴. More importantly, the authors noted the presence of an association in some retrospective studies, while it was absent in most of the prospective studies⁹⁴.

Placenta-mediated complications

Placenta-mediated complications, such as *abruptio placentae* and hematoma and late pre-eclampsia/intra-uterine growth restriction (IUGR), have been reported as complications of APS patients in various case reports and cohorts^{96,97}. While pre-eclampsia and IUGR before the 34th week of gestation are included in the revised criteria¹, those occurring afterward are not. It is hypothesized that early pregnancy complications are related to a direct inhibitory effect of aPL on the trophoblast cells, while late manifestations are attributable to placental dysfunction due to thrombotic and inflammatory changes⁹⁸. In the *Summary of the 9th meeting of the European Forum on aPL*, the concept of obstetric morbidity associated with APS (OMAPS) was discussed, including some of these manifestations: two miscarriages, late pre-eclampsia, *abruptio placentae*, late premature birth, and more than two unexplained IVF failures⁹⁹. Nevertheless, a meta-analysis attempting to clarify the association between aPL and some late placenta-mediated complications (i.e., late fetal loss, pre-eclampsia, IUGR, and placental abruption) was unable to establish a categorical relationship due to significant heterogeneity and underpowered studies¹⁰⁰. The EUROAPS registry has gathered data regarding these obstetric patients with non-criteria manifestations^{101,102} and, in a publication with 1000 obstetric APS patients, two spontaneous abortions before 10 weeks of gestation were present in 9.5% of patients, IUGR after 34 weeks of gestation in 4.7%, pre-eclampsia after 34 weeks of gestation in 4.6%, placental hematoma in 1.3%, and *abruptio placentae* in 1%¹⁰². Nonetheless, the impact of each individual manifestation in APS patient is still unclear.

Conclusion

From the analysis of the available evidence regarding the different non-criteria manifestations it is notorious that, although relevant, their association with APS/aPL is still unclear or scarcely characterized in most cases. This notion reinforces the need for well-designed studies evaluating specific manifestations in homogeneous APS populations.

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Conflicts of interest

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