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Risk Factors for Antiphospholipid Syndrome in Women of Reproductive and Different Ages

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Annotation: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies. APS can present with a variety of clinical phenotypes, including thrombosis in the veins, arteries and microvasculature as well as obstetrical complications. The pathophysiological hallmark is thrombosis, but other factors such as complement activation might be important. Prevention of thrombotic manifestations associated with APS includes lifestyle changes and, in individuals at high risk, low-dose aspirin. Prevention and treatment of thrombotic events are dependent mainly on the use of vitamin K antagonists. Immunosuppression and anticomplement therapy have been used anecdotally but have not been adequately tested. Pregnancy morbidity includes unexplained recurrent early miscarriage, fetal death and late obstetrical manifestation such as pre-eclampsia, premature birth or fetal growth restriction associated with placental insufficiency. Current treatment to prevent obstetrical morbidity is based on low-dose aspirin and/or low-molecular-weight heparin and has improved pregnancy outcomes to achieve successful live birth in >70% of pregnancies. Although hydroxychloroquine and pravastatin might further improve pregnancy outcomes, prospective clinical trials are required to confirm these findings.

Keywords: antiphospholipid antibodies, antiphospholipid syndrome, complications of pregnancy, catastrophic antiphospholipid syndrome.

More than 40 years after discovery, APS remains one of the most mysterious syndromes in modern medicine. APS is a heterogeneous systemic syndrome and at the same time an autoimmune disease, acquired immune thrombophilia, and thromboinflammatory disease. Clinical manifestations are caused by antibody-mediated activation of key target cells and modulation of several major biological systems through the interaction of these antibodies with various cofactors and special cell surface receptors. Such interactions lead to the activation of complement on cell surfaces, activation of neutrophils and monocytes, release of antiangiogenic factors, reactive oxygen species (ROS), TNF-a, activation of blood coagulation, inflammation, and NETosis (neutrophil extracellular trap formation). Because of the variable clinical manifestations of APS, it is often called “chameleon syndrome”. However, not all clinical manifestations are included in the criteria for APS, nor are antiphospholipid antibodies, which are divided into criteria (lupus anticoagulant (LA), anticardiolipin (ACL), anti-β2-glycoprotein I (anti-β2GPI)) and non-criteria (ant annexin A2, ant vimentin/cardiolipin complex, ant annexin A5, ant phosphatidylethanolamine, ant phosphatidylinositol, etc.). Therefore, the classification criteria for APS are revised from time to time.

The so-called Sydney or revised Sapporo criteria for APS are very well known and include clinical criteria (venous and/or arterial thrombosis, and/or microcirculatory thrombosis, and/or morbidity in pregnant women) and laboratory criteria (LA, and/or aCL, and/or anti-β2GPI antibodies). APS is confirmed if at least one clinical and one laboratory criteria are present. In 2023, new classification criteria for APS were developed and proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). The supplemented clinical criteria are divided into six domains and laboratory criteria into two domains. The proposed new APS criteria are highly specific (99% versus 86% of the current Sapporo criteria), risk stratified, and hierarchically clustered [1]. Due to the heterogeneity of clinical manifestations and pathogenetic mechanisms, APS is conventionally divided into “pure” obstetric (o-APS) and thrombotic antiphospholipid syndrome (t-

APS). O-APS is characterized by recurrent fetal loss, intrauterine death, neonatal death, placental insufficiency, preterm birth, placental abruption, severe preeclampsia, and HELLP syndrome. Thrombosis is less typical for o-APS, although o-APS and t-APS can be combined. Currently, pediatric and even neonatal APS are also distinguished. Children may also develop an extreme form of APS, catastrophic antiphospholipid syndrome (CAPS), as the first manifestation of the syndrome.

Catastrophic antiphospholipid syndrome (CAPS) is a rare and life-threatening condition, characterized by thromboses with the development of multiple organ failure [2]. The classification criteria for CAPS are: damage to three or more organs, rapid development of clinical manifestations, histopathological patterns of small vessel occlusion and the circulating APLA (Table 1) [3,4]. The disease was first described by S. Greis man in 1991. However, this pathology is also called Asherson syndrome in honor of the doctor who first introduced the term "CAPS" in 1992 [5]. In the 1980s, while working at the Hammersmith hospital, Ronald Asherson began collecting and describing rare cases of CAPS. Together with Ricardo Cervera, they initiated the creation of a worldwide database. The result of their work was the CAPS international register, where everyone can add clinical cases [6]. Although CAPS develops in less than 1% of patients with APS, it is a life-threatening condition that requires early diagnosis and immediate treatment [7].

During pregnancy, an additional organ, placenta, appears, therefore placental thrombosis should also be considered in the diagnosis of CAPS. The data sources for primary articles were the following databases: PubMed, Web of Science, the Cochrane Database, Wiley Online Library, ScienceDirect, Elibrary, Medline, ResearchGate, and Dissertation Abstracts International. The search strategy used a combination of free text search, Medical Exploded Subject Headings (MESH), and all synonyms of the following terms: "catastrophic antiphospholipid syndrome" and "CAPS" with "pathophysiology", "treatment", "epidemiology", "diagnosis", and equivalent terms in other languages.

Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or adverse pregnancy outcome in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPLs). Preeclampsia complicates about 10–17% of pregnancies with APS. However, only early onset preeclampsia (<34 weeks of gestation) belongs to the clinical criteria of APS. The similarities in the pathophysiology of early onset preeclampsia and APS emphasize an association of these two syndromes. Overall, both are the result of a defective trophoblast invasion and decidual transformation at early gestation. Women with APS are at increased risk for prematurity; the reasons are mostly iatrogenic due to placental dysfunction, such as preeclampsia or FGR. Interestingly, women with APS have also an increased risk for preterm delivery, even in the absence of FGR and preeclampsia, and therefore it is not indicated but spontaneous. The basic treatment of APS in pregnancy is low-dose aspirin and low-molecular-weight heparin. Nevertheless, up to 20–30% of women develop complications at early and late gestation, despite basic treatment. Several additional treatment options have been proposed, with hydroxychloroquine (HCQ) being one of the most efficient. Additionally, nutritional interventions, such as intake of vitamin D, have shown promising beneficial effects. Curcumin, due to its antioxidant and anti-inflammatory properties, might be considered as an additional intervention as well.

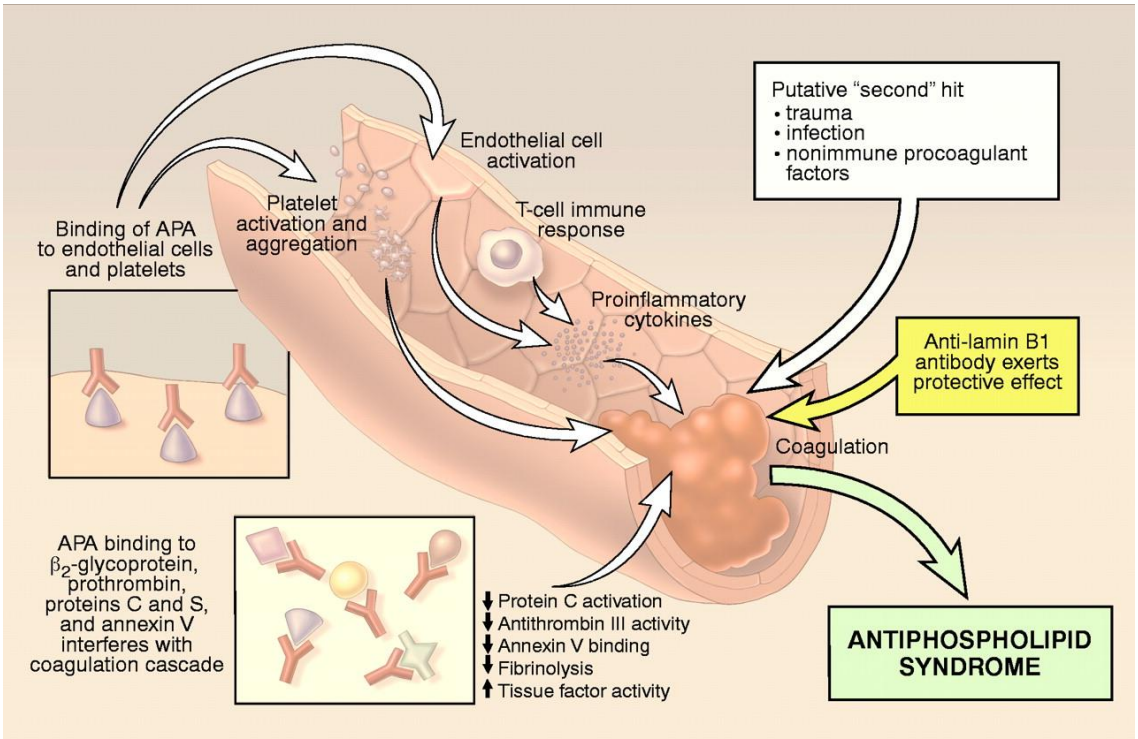

Figure 1: Pathogenic mechanisms in antiphospholipid syndrome.

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies/aPLs (anticardiolipin antibodies/ACLA, lupus anticoagulant/LA, and anti-ß2-glycoprotein/anti-ß2-GPI). These antibodies are associated with arterial and/or venous thromboses and with various complications in early and late pregnancy [1,2].

Patients with solely obstetric complications but without any thrombotic events in the past are described as patients with obstetric antiphospholipid syndrome (OAPS) [3,4]. Clinical manifestations of OAPS are complications in early and late gestation, including recurrent early fetal loss before 10 weeks of gestation; late fetal loss at or beyond 10 weeks of gestation; or placental dysfunction in second and third trimester, such as fetal growth restriction, preeclampsia, or fetal death [1,2].

Preeclampsia is a pregnancy-specific multiorgan disorder, complicating 3–5% of all pregnancies [13]. Preeclampsia is diagnosed based on a new onset of hypertension and proteinuria or end organ damage after 20 weeks of gestation [13]. It presents itself in two different phenotypes, depending on the onset of symptoms as well as clinical manifestation [13]. Early onset of preeclampsia/EOP occurs before 34 weeks of gestation, and late onset preeclampsia/LOP after 34 weeks of gestation [13]. The basic treatment of APS in pregnancy is low-dose aspirin (LDA) and low-molecular-weight heparin (LMWH). However, approximately 20–30% of women will suffer from pregnancy complications in spite of this treatment [22]. An interesting fact is that the treatment is more efficient for the prevention of preeclampsia or other forms of placental dysfunction in comparison to recurrent fetal loss [23]. Several additional treatment options have been proposed, with hydroxychloroquine (HCQ) being one of the most efficient [24,25].

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder characterised by thrombosis and the presence of antiphospholipid antibodies (aPL): lupus anticoagulant and/or IgG/IgM anti-β2-glycoprotein I and anticardiolipin antibodies. APS carries significant morbidity for a relatively young patient population from recurrent thrombosis in any vascular bed (arterial, venous, or microvascular), often despite current standard of care, which is anticoagulation with vitamin K antagonists (VKA). Platelets have established roles in thrombosis at any site, and platelet hyperreactivity is clearly demonstrated in the pathophysiology of APS. Together with excess thrombin generation, platelet activation and aggregation are the common end result of all the pathophysiological pathways leading to thrombosis in APS. However, antiplatelet therapies play little role in APS, reserved as a possible

option of low dose aspirin in addition to VKA in arterial or refractory thrombosis. This review outlines the current evidence and mechanisms for excessive platelet activation in APS, how it plays a central role in APS-related thrombosis, what evidence for antiplatelets is available in clinical outcomes studies, and potential future avenues to define how to target platelet hyperreactivity better with minimal impact on haemostasis.

Many pathophysiological processes have been shown to act in concert to cause APS-related thrombosis, including activation and recruitment of multiple cell types—endothelial cells, platelets, leukocytes—as well as the coagulation and complement systems (Figure 1). This complex interplay manifests in heterogeneous thrombosis, which can occur in any vascular bed; venous, arterial, or microvascular. While the concept of targeting the many pathophysiological processes is overwhelming and would potentially have substantial adverse effects, clinical focus has mainly been on targeting coagulation factors. However, platelets have been shown to have a significant role in thromboses within any vascular bed, raising the consideration that platelets could have a central role in APS [12,13]. Thromboses within arteries are known to be mainly driven by platelets, typically initiated by adhesion to pathologically exposed subendothelial collagen, followed by platelet activation and aggregation [14]. Venous thrombosis has traditionally been considered to be fibrin and red cell rich, with intact endothelium and a lesser role for platelets. However, more recently, in vitro models have demonstrated venous thrombus extension driven by a procoagulant subpopulation of platelets in a glycoprotein (GP)VI-dependent manner [15]. This procoagulant platelet subpopulation forms after strong stimulation, most potently with thrombin and collagen, which causes sustained raised cytosolic calcium, leading to translocation of phosphatidylserine (PS) from the inner to the outer platelet membrane, providing a negatively charged surface for coagulation factor complexes to form and generate a burst of thrombin to drive fibrin formation [16]. This platelet subpopulation is more implicated in thrombosis than haemostasis, making it an attractive target for novel therapeutics. Microvascular thrombosis is characterised by fibrin and platelet-rich thrombi, with a critical role for the procoagulant properties of platelets, and their interaction with neutrophils, now apparent [17].

Antiphospholipid syndrome (APS) is a complex thrombo-inflammatory autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL). Women with APS are at high risk of recurrent early pregnancy loss as well as late obstetrical complications—premature birth due to placental insufficiency or severe preeclampsia. Accumulating evidence implies that vascular thrombosis is not the only pathogenic mechanism in obstetric APS, and that the direct negative effect of aPL on the placental cells, trophoblast, plays a major role. In this review, we summarize the current findings regarding the potential mechanisms involved in aPL-induced trophoblast dysfunction. Introduction on the APS and aPL is followed by an overview of the effects of aPL on trophoblast—survival, cell function and aPL internalization. Finally, the implication of several non-coding RNAs in pathogenesis of obstetric APS is discussed, with special emphasis of their possible role in trophoblast dysfunction and the associated mechanisms.

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent arterial, venous and microvasculature thrombosis and/or obstetrical complications associated with circulating antiphospholipid antibodies (aPL) [1,2]. The diagnosis and classification of APS is based on the Sydney 2006 updated international classification criteria consensus [3]. According to these criteria, at least one of the clinical conditions and persistent detection of at least one of the criteria aPL have to be present for APS diagnosis [3] (Table 1). The autoantibodies accepted for the laboratory criteria include lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I IgG and/or IgM antibodies (Table 1). APS can be an isolated disease when it is defined as primary. Secondary APS represents coexistence of APS with some other autoimmune disorder, usually systemic lupus erythematosus (SLE) [1,4]. APS/SLE patients account for around 30% of all APS cases [5,6,7,8].

The estimated APS annual incidence and prevalence in the general population ranges between 1 and 2 cases per 100,000 persons and between 40 and 50 per 100,000 persons, respectively [9]. Most of the APS patients are diagnosed during the reproductive period with the mean age of diagnosis between 30 and 40 years for women, as several studies presented [6,8,9,10,11]. Moreover, APS is found to be more

frequent in females especially when considering patients with secondary APS associated with SLE [6,9,10]. However, some studies found that there was no difference in APS frequency between sexes [7,8,9].

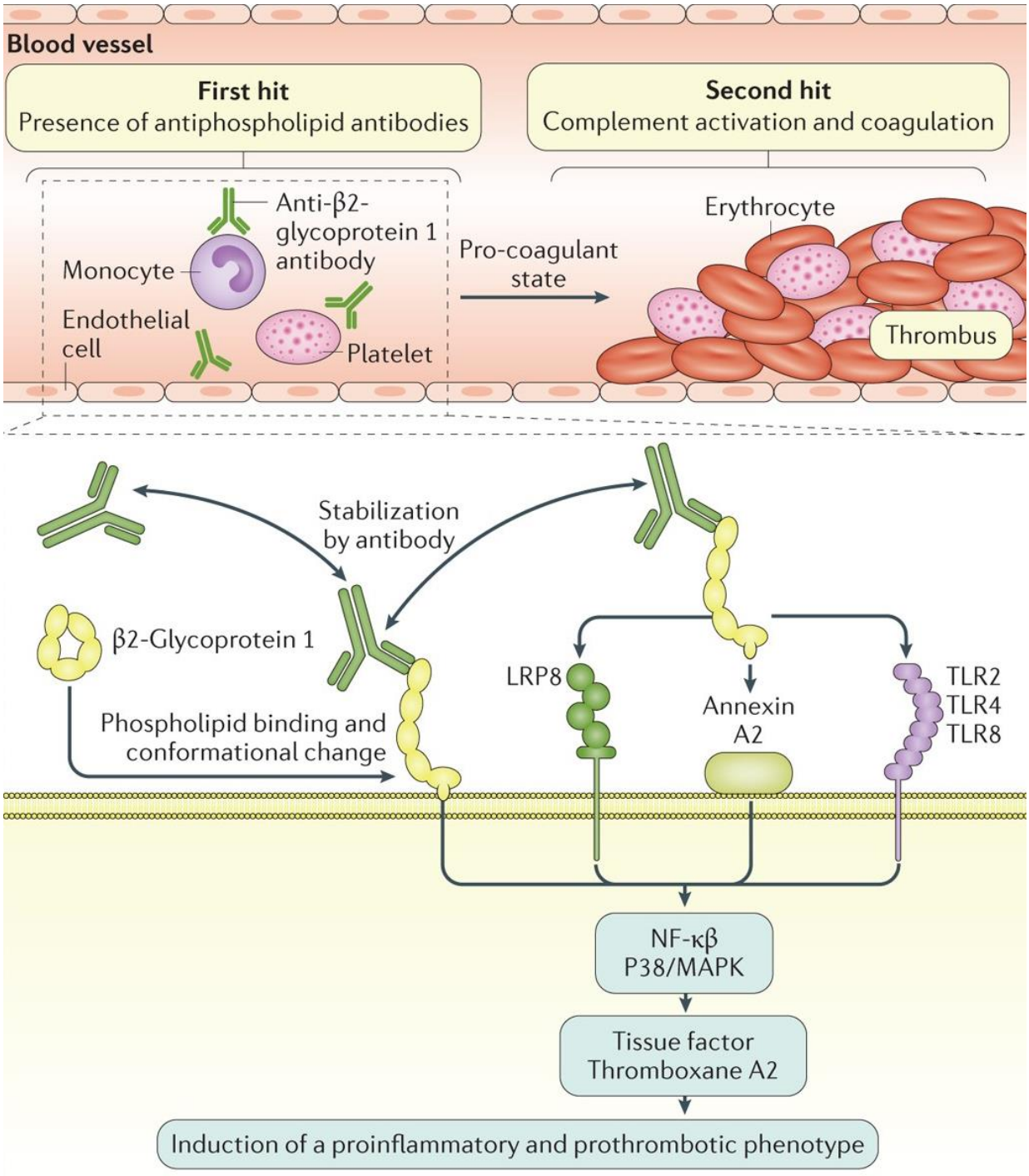

Figure 2: Pathophysiology of antiphospholipid antibody-associated thrombosis.

According to the clinical manifestations, two main subtypes of APS could be distinguished: vascular and obstetrical APS [12]. Vascular APS is mainly characterized by venous, arterial and small vessel thrombotic events in different organs [12]. Obstetrical APS (OAPS) is manifested with pregnancy morbidities and lower frequency of thrombotic events [12,13,14,15]. Distinct molecular signatures in these two APS subtypes were also found [16]. The most prevalent pregnancy complications in OAPS are early recurrent pregnancy loss (RPL), unexplained fetal death and stillbirth [5,14,17,18]. Complications in later stages of pregnancy including premature birth, preeclampsia (PE) and intrauterine growth restriction (IUGR) are also common for OAPS patients [5,14,17,18]. The original

historic assumption was that complications in OAPS were associated with placental thrombotic phenomena [19]. However, experimental data accumulating over the past couple of decades have shown that inadequate placentation due to multiple detrimental effects of aPL on trophoblast, specialized placental cells, as well as other cell types of the placenta and uterus is a major cause of pregnancy morbidities in OAPS [12,14].

The gold standard treatment of APS is low dose aspirin combined with low molecular weight heparin at prophylactic or therapeutic doses, depending on a history of blood clots and previous complications during pregnancy [20,21]. In about 20–30% of OAPS patients, standard treatment does not give satisfactory results and they suffer from recurrent pregnancy complications [22]. There are several treatment options reserved for refractory OAPS including hydroxychloroquine, low-prednisone dose, intravenous immunoglobulins or plasma exchange [21]. Biologic therapies using anti-TNF-α antibodies in combination with standard treatment gave promising results for the treatment of refractory OAPS [22,23]. Recently, aPL-induced epigenetic modifications, including dysregulated expression of non-coding RNAs, emerged as key contributors to the APS progression as well as potential additional biomarkers and therapeutic targets in APS [24,25].

In this review, following the Introduction, we will briefly present general information on aPL types, their antigens and general mechanisms of action. Further, we will focus on aPL-induced effects on trophoblast cell survival and function. Finally, we will present current knowledge on non-coding RNAs as mediators of aPL-induced obstetric complications.

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombotic and non-thrombotic macro- and microvascular manifestations and pregnancy complications in the setting of persistent antiphospholipid antibodies (aPL), namely anticardiolipin antibodies, anti-β2 glycoprotein-I antibodies and lupus anticoagulant. Four decades after its first description, APS prevalence and incidence are still not completely understood due to the limited number of well-designed, population-based multi-ethnic studies. Furthermore, despite decades of efforts to standardise aPL immunoassays, considerable intraassay and interlaboratory variances in aPL measures still exist. Large multicentre APS cohorts have shown a 10-year survival of ∼91% and the presence of catastrophic APS occurs in about 1% of the entire population, associated with a 50% mortality rate. Clinically, any organ can be affected in the context of large, medium or small vessel (artery and/or vein) thrombosis. Macrovascular thrombosis is the hallmark of the disease and veins are more frequently affected than arteries. Deep vein thrombosis/pulmonary embolism thromboembolic disease is the most common APS manifestation, while stroke and transient ischaemic attack are the most frequent arterial thrombosis events. Myocardial infarction can also occur and contributes to increased mortality in APS. A minority of patients present with thrombosis affecting the intraabdominal organs, including the liver, spleen, small and large bowel, and the kidneys. Microvascular thrombosis, including APS nephropathy, chronic skin ulcers and livedoid vasculopathy represent a diagnostic challenge requiring histologic confirmation. In this narrative review we summarize the available evidence on APS epidemiology, focusing on the description of the prevalence of macro- and microvascular manifestations of the disease.

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by pregnancy morbidity, venous and arterial thrombosis and/or microvascular manifestations in the presence of antiphospholipid antibodies (aPL) [1]. Although APS was recognized almost four decades ago, its prevalence and incidence, as well as the prevalence of aPL in different populations is still not fully defined due to the paucity of well-designed population-based multi-ethnic studies [2, 3]. Furthermore, despite decades of efforts for standardized aPL immunoassays, intraassay and interlaboratory variations in aPL measurements still exist, further challenging the available epidemiological data [4, 5].

In a population-based study of newly diagnosed APS patients between 2000 and 2015 in Olmsted County, Minnesota, the annual incidence of APS was 2.1 [95% confidence interval (CI): 1.4–2.8] per 100 000 population, and the estimated prevalence was 50 per 100 000 adults [6]. Conflicting reports

exist regarding the prevalence of APS in males and females [6, 7], which can be attributed to different population characteristics among studies, e.g., primary vs secondary APS rates and racial/ethnic composition. In a recent review article including data from six population-based studies, the estimated incidence and prevalence for APS ranged from 1 to 2 and from 40 to 50 cases per 100 000 adults, respectively [2].

Regarding the prevalence of the clinical manifestations included in the APS classification criteria [1], data from the two largest multicentre registries so far, the EuroPhospholipid Project and the AntiPhospholipid Syndrome Alliance For Clinical Trials and International Networking (APS ACTION) registries, showed that venous thromboembolic disease, including deep venous thrombosis (DVT) and/or pulmonary embolism, and acute cerebrovascular events [stroke and transient ischaemic attacks (TIA)], are the most common thrombotic manifestations of APS [8, 9]. Additionally, several extra-criteria clinical features have been reported among APS patients with varying prevalence, including thrombocytopenia, APS nephropathy, valvular heart disease, skin ulcers and livedo reticularis [10]. Less than 1% of patients with APS develop catastrophic APS (CAPS), a life-threatening thromboembolic disease with a mortality rate of ∼50%, affecting three or more organ systems within 1 week [11, 12]. The survival probability at 10 years in the EuroPhospholipid registry including 1000 APS patients, the largest registry so far in APS, was 90.7% [13].

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