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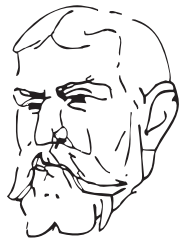
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REVIEW ARTICLE

Current aspects of the etiopathogenesis of antiphospholipid syndrome and its clinical manifestations

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ABSTRACT

Antiphospholipid syndrome is a systemic autoimmune disorder characterized by the persistent presence of antiphospholipid antibodies and a predisposition to arterial, venous, and microvascular thrombotic manifestations. In this article, the authors analyzed the available literature sources in the PubMed, Scopus, Web of Science, and Google Scholar databases for the period from 2019 to 2026, focusing on the epidemiological, gender-related, etiopathogenetic, clinical, and diagnostic aspects of antiphospholipid syndrome. Antiphospholipid syndrome emerges as a systemic immune-vascular nosological entity in which cerebrovascular and cardiovascular manifestations constitute the main clinical phenotype and determine the long-term prognosis of the disease. Understanding antiphospholipid syndrome as a unified immune-coagulation process is of fundamental importance for clinical practice, as it provides a basis for more accurate risk stratification, early identification of patients with a high probability of severe vascular complications, and the development of pathogenetically substantiated therapeutic methods targeting not only the coagulation cascade but also the immune and inflammatory components of the disease. Such an integrative approach is fundamental to optimizing treatment and improving the prognosis of patients with antiphospholipid syndrome.

KEY WORDS: antiphospholipid syndrome, literature data analysis, etiopathogenesis, clinical manifestations.

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INTRODUCTION

Antiphospholipid syndrome is a systemic autoimmune pathology characterized by the persistent presence of antiphospholipid antibodies and a predisposition to arterial, venous, and microvascular thrombotic manifestations [1, 2]. Its pathogenesis extends beyond the classical concepts of thrombophilia and combines immune, coagulation, and inflammatory mechanisms, forming a systemic process [3]. The relevance of an in-depth study of antiphospholipid syndrome is determined by the high clinical significance of its vascular manifestations, primarily cerebrovascular, cardiovascular, and obstetric complications, which determine the prognosis, level of disability, and mortality of patients. Particular attention should be paid to the fact that severe thrombotic complications in antiphospholipid syndrome often occur at a young age and in the absence of traditional cardiovascular risk factors, which complicates their early diagnosis and prevention [4].

However, despite the substantial body of accumulated data on the immunopathogenesis of antiphospholipid syndrome, the scientific literature is still dominated by a fragmented analysis of individual clinical manifestations without sufficient emphasis on their pathogenetic unity. Current concepts of immunothrombosis allow cerebrovascular, cardiac, obstetric, and other organ lesions to be regarded as different manifestations of a single systemic process; however, such a perspective requires further generalization and conceptual understanding. The relevance of this study lies in the systematic analysis of antiphospholipid syndrome from the perspective of the unity of immunothrombotic mechanisms, with particular emphasis on obstetric manifestations as a distinct pathogenetic phenotype, as well as their relationship with cerebrovascular and cardiovascular lesions, which provides a basis for a more comprehensive assessment and improvement of current methods for the diagnosis, treatment, and prevention of antiphospholipid syndrome.

AIM

The aim of the study is to summarize current concepts of antiphospholipid syndrome as a systemic immune-vascular disorder, taking into account the pathogenetic unity of its manifestations, which constitute the main clinical manifestations and determine the prognosis of the disease.

MATERIALS AND METHODS

The study analyzed literature data published between 2019 and 2026 addressing the epidemiological, gender-related, etiopathogenetic, clinical, and diagnostic aspects of antiphospholipid syndrome. The literature search was conducted in the PubMed, Scopus, Web of Science, and Google Scholar databases.

REVIEW AND DISCUSSION

Antiphospholipid syndrome is a rare systemic autoimmune disease, the epidemiological study of which is complicated by a combination of clinical heterogeneity, variability in diagnostic criteria, and differences between the presence of antiphospholipid antibodies and clinically manifest syndrome [5, 6]. Review and population-based studies agree that the prevalence of antiphospholipid syndrome itself in the general population is low, whereas seropositivity for antiphospholipid antibodies is considerably more common and is not always accompanied by the development of clinical manifestations [5, 7].

According to a population-based registry study, the incidence of antiphospholipid syndrome is approximately several cases per 100,000 persons per year, while its prevalence is several dozen cases per 100 000 population, confirming the rare nature of this disease [8]. Similar rates were also obtained in a nationwide population-based study in South Korea, where the standardized incidence and prevalence of antiphospholipid syndrome remained consistently low throughout the observation period, despite increased awareness and improved diagnosis [9]. The synthesis of these data in recent reviews suggests that substantial differences between countries more often reflect methodological differences between studies rather than true epidemiological disparities [5].

Analysis of the age and gender distribution demonstrates a clear predominance of women among patients with antiphospholipid syndrome, which is consistent with the general patterns of autoimmune diseases [1, 7]. The highest frequency of diagnosis occurs in young and middle-aged individuals, with a particular concentration of cases among women of reproductive age, which is partly associated with the obstetric manifestations of the syndrome and more active screening in this population [10, 11]. At the same time, population-based data indicate that antiphospholipid syndrome may first manifest at any age, including old age, although the incidence of new cases is lower in older age groups [8].

Geographic variability in the prevalence and incidence of antiphospholipid syndrome remains a matter of debate, as studies conducted in Europe, North America, and Asia demonstrate generally comparable rates when standardized diagnostic criteria are applied [9]. At the same time, in regions with limited access to laboratory diagnostics and specialized medical care, the prevalence of the syndrome may be underestimated, as supported by individual regional reports, particularly those concerning pregnant women in African countries [12]. These data emphasize the influence of organizational and social factors on the detection of antiphospholipid syndrome, rather than solely true differences in its biological prevalence.

In modern medicine, antiphospholipid syndrome is regarded not as a collection of individual clinical manifestations but as an independent autoimmune nosological entity that develops at the intersection of immunological abnormalities and characteristic vascular and obstetric disorders [13]. The defining feature of the syndrome is not the isolated presence of thrombosis or other manifestations, but their combination with the persistent presence of antiphospholipid antibodies, which gives the clinical manifestations a systemic and recurrent character [14]. It is this conceptual unity of clinical and laboratory features that allows antiphospholipid syndrome to be regarded as a distinct pathological entity rather than as a complication of other diseases or a coincidental combination of symptoms.

Etiologically, antiphospholipid syndrome is a multifactorial disease, the development of which is determined by a combination of genetic predisposition, acquired immune abnormalities, and the effects of external triggering factors. At the current stage of understanding antiphospholipid syndrome, its etiology is not regarded as the result of the isolated influence of a single factor but is interpreted within a complex model that combines immunological determinants with the conditions for the development of a pathological response [15]. Thus, the central etiological link in the development of antiphospholipid syndrome is the formation of antiphospholipid antibodies, primarily antibodies against β2-glycoprotein I (β2GPI), which arise as a result of impaired immune tolerance to endogenous phospholipid-binding proteins. Structural changes in β2GPI caused by its binding to negatively charged phospholipids or by oxidative stress are believed to pro-

mote the exposure of immunodominant epitopes and the initiation of an autoimmune response [14]. Thus, autoantibody formation is not a random phenomenon but rather the result of specific molecular conditions that provide the basis for immune aggression.

An important component of the etiology of antiphospholipid syndrome is genetic predisposition, which determines individual susceptibility to the formation of antiphospholipid antibodies and thrombotic complications. Although a specific «antiphospholipid syndrome gene» has not been identified, the role of genetic factors is supported by associations with certain HLA alleles, as well as with genes involved in the regulation of the immune response and hemostasis [16]. However, the genetic background is regarded not as a determining factor but as a modulating factor that increases the likelihood of the development of the pathological process in the presence of additional triggers.

Etiologically significant external factors include infectious agents, medications, and other conditions capable of inducing or temporarily increasing the production of antiphospholipid antibodies. The infection-induced presence of antiphospholipid antibodies is described as a consequence of molecular mimicry or nonspecific activation of the immune system; however, only in a proportion of cases does it progress to clinically significant antiphospholipid syndrome [17]. This observation emphasizes the fundamental difference between the transient presence of antiphospholipid antibodies and antiphospholipid syndrome itself as a nosological entity.

In this context, the «second hit» concept is of key etiological importance, according to which the presence of antiphospholipid antibodies creates only a potential predisposition to thrombotic manifestations, whereas their clinical development requires an additional triggering factor, such as inflammation, infection, hormonal changes, surgical interventions, or vascular injury [18]. This model explains the variability in the clinical course of antiphospholipid syndrome and the intermittent nature of thrombotic complications.

Currently, primary and secondary antiphospholipid syndromes are traditionally distinguished. Primary antiphospholipid syndrome is diagnosed in the absence of another systemic autoimmune disease, whereas secondary antiphospholipid syndrome develops in the setting of systemic lupus erythematosus or other immune-inflammatory conditions. This distinction has not only formal but also pathophysiological and clinical significance, as secondary antiphospholipid syndrome is more often associated with a broader spectrum of immune abnormalities and a more complex clinical course [1]. At the same time, recent reviews emphasize that, in terms of the mechanisms of thrombosis and immune activation, primary and secondary forms of the syndrome share many common features, which calls into question their strict distinction as separate diseases [19, 20].

A significant methodological challenge remains the relationship between so-called «classical» antiphospholipid syndrome, which meets the current classification criteria, and the spectrum of non-criteria manifestations that fall outside the formal diagnostic framework [14].

The classification criteria were developed primarily to standardize research and do not encompass all possible clinical phenotypes of the syndrome, as confirmed by data from multinational cohort studies [21]. In this context, the concept of «non-criteria» antiphospholipid syndrome is increasingly used to reflect clinical reality but requires cautious application to avoid unjustified expansion of the diagnostic criteria. Current expert publications emphasize that non-criteria manifestations may have prognostic significance; however, they should not, by themselves, be automatically interpreted as confirmation of the presence of the syndrome [23].

Also important for understanding antiphospholipid syndrome is a clear distinction between the isolated presence of antiphospholipid antibodies and clinically manifest syndrome. Population-based studies and recent reviews consistently indicate that the presence of antiphospholipid antibodies in blood serum is considerably more prevalent than the syndrome itself, and most antiphospholipid antibodies-positive individuals never develop clinical manifestations characteristic of antiphospholipid syndrome [1]. This distinction is of fundamental importance for both epidemiological assessment and clinical practice, since equating antibody positivity with the syndrome leads to an overestimation of prevalence rates and potential overdiagnosis [23]. Therefore, in current conceptual studies, antiphospholipid syndrome is defined as the result of the interaction between immunological predisposition and additional triggering factors, rather than as an inevitable consequence of the presence of antiphospholipid antibodies [24].

Current diagnosis of antiphospholipid syndrome is based on a comprehensive assessment of clinical manifestations and laboratory findings. In 2023, the American College of Rheumatology and the European Alliance of Associations for Rheumatology proposed new classification criteria requiring the presence of at least one clinical manifestation of antiphospholipid syndrome and one positive antiphospholipid antibody test performed within three years of the onset of clinical manifestations [6]. Further assessment is performed using a scoring system that takes into account clinical features (venous and arterial thrombosis, microvascular and obstetric manifestations, heart valve involvement,

and hematological abnormalities) and laboratory parameters (lupus anticoagulant, anticardiolipin antibodies, and anti-β2GPI antibodies) [25]. To establish antiphospholipid syndrome, at least three points must be obtained separately for the clinical and laboratory criteria. Another general diagnostic algorithm for antiphospholipid syndrome involves the assessment of clinical manifestations, laboratory testing for the main antiphospholipid antibodies, and repeat testing after 12 weeks to confirm their persistence [23]. Particular attention is also paid to risk stratification, as the most unfavorable prognosis is more characteristic of patients with lupus anticoagulant and high titers of anticardiolipin and anti-β2GPI antibodies [1].

Cerebrovascular and cardiovascular manifestations of antiphospholipid syndrome result from an integrated immune-coagulation process in which autoantibodies, blood cells, the endothelium, complement, and inflammation act as a mutually reinforcing system that stabilizes the prothrombotic state. This pathogenetic chain should be regarded not as a sum of isolated abnormalities but as a form of so-called immunothrombosis, in which thrombus formation becomes the effector phase of chronic immune activation [26].

The formation and functional activity of anti-β2GPI antibodies are considered the key immunopathogenetic link, conferring specificity on antiphospholipid syndrome and explaining its systemic thrombotic potential [27]. According to current concepts, β2GPI acts as a central cofactor that ensures the binding of immune complexes to cell surfaces and the translation of the autoimmune signal into a procoagulant response [28]. Anti-β2GPI antibodies increase tissue factor expression in endothelial cells and monocytes, thereby promoting activation of the coagulation cascade, enhancing thrombin generation, and facilitating coagulation [19].

For cerebral and cardiac vessels, the key factor is that, in response to antiphospholipid antibodies, the endothelium shifts from a vasoprotective state to an activated, prothrombotic phenotype [3]. This activation is accompanied by increased expression of adhesion molecules, enhanced interactions with leukocytes and platelets, and alterations in the local regulation of hemostasis, which promote the adhesion of cellular aggregates and the formation of a thrombotic substrate. Importantly, antiphospholipid antibodies are capable of inducing proinflammatory and procoagulant signals in the endothelium, causing the vascular wall itself to actively support thrombogenesis [18, 20]. In this sense, endothelial dysfunction is not merely a «background» condition but a central link that directly connects the systemic autoimmune trigger with local cerebrovascular and coronary manifestations.

In parallel with the endothelium, platelet activation is an important factor contributing to the predisposition to thrombosis; in antiphospholipid syndrome, it exhibits features of persistent hyperreactivity and may be regarded as one of the mechanisms maintaining the risk of arterial manifestations and complications. In patients with primary antiphospholipid syndrome, markers of increased platelet activation are detected, which is consistent with the concept of enhanced aggregation and increased propensity for thrombus formation [30]. Platelet activation is pathogenetically significant not only because of aggregation but also because of the involvement of platelets in intercellular communication, particularly in their interactions with the endothelium and leukocytes and in the maintenance of local inflammation [26].

A link that amplifies and «consolidates» vascular injury is activation of the complement system, which in antiphospholipid syndrome is regarded as a universal mechanism for amplifying the immune signal and coagulation response. Complement can exacerbate endothelial dysfunction, increase the expression of tissue factor (TF, CD142), and thereby integrate immune reactions with the blood coagulation cascade [31]. In current models of pathogenesis, complement is regarded not as a peripheral component but as a fully integrated link that mediates the transition from antibody-mediated activation to clinically significant thrombosis, including microvascular lesions [32].

Inflammation in antiphospholipid syndrome is not merely a secondary response to thrombosis but is a component of the aforementioned conceptual pathogenetic chain of «immune activation + endothelial dysfunction + coagulation». The concept of immunothrombosis emphasizes that elements of innate immunity, proinflammatory mediators, and cellular effectors form a microenvironment in which thrombus formation becomes a physiologically «supported» response [33]. In this context, antiphospholipid syndrome is regarded as a condition in which the immune response and hemostasis function as a unified system, while its vascular manifestations represent a predictable final manifestation of systemic imbalance [1].

The clinical and pathogenetic reality of the systemic risk of thrombotic manifestations and complications is confirmed by data indicating a high risk of their recurrence in patients with antiphospholipid syndrome, particularly in high-risk groups, which indicates the persistence of pathogenetic imbalance even during treatment. This predisposition to recurrent complications is consistent with the concept of sustained endothelial activation maintained by autoantibodies and inflammatory mechanisms [23].

The mechanistic unity of arterial, venous, and microvascular thrombosis in antiphospholipid syndrome requires particular attention, as it allows for an understanding of the systemic nature of the vascular manifestations of the disease and explains their occurrence in different vascular beds in the presence of a common immunological background. Unlike classical thrombotic conditions, in which the localization of thrombosis is often determined predominantly by hemodynamic factors or structural characteristics of the vascular wall, in antiphospholipid syndrome the decisive role is played by systemic immunopathogenetic activation, which creates a universal prothrombotic environment regardless of vessel type [26, 34]. Despite substantial differences between arterial, venous, and microvascular circulation, particularly in terms of flow velocity, pressure, and other parameters, a common pathogenetic mechanism is reproduced in all these vessels in antiphospholipid syndrome. Its main components include the persistent effects of antiphospholipid antibodies, activation of vascular wall cells and blood cells, development of endothelial dysfunction, involvement of platelets and the complement system, as well as the formation of a local proinflammatory microenvironment that maintains and enhances thrombus formation [19]. The recurrence of this set of mechanisms across different vascular beds indicates that thrombosis in antiphospholipid syndrome is a consequence not of local injury but of a systemic immune-coagulation imbalance. Therefore, this approach allows arterial, venous, and microvascular thrombosis to be regarded not as separate phenotypes but as different clinical manifestations of a single pathogenetic process modified by local vascular conditions [35]. In this context, antiphospholipid syndrome fundamentally differs from «classical» inherited or acquired thrombophilias, which are characterized by the predominance of defects in the coagulation cascade in the absence of a pronounced immune component.

Thus, the pathogenetic mechanisms of antiphospholipid syndrome discussed above form a universal immune-dependent basis for the development of vascular lesions in various organs and tissues. At the same time, the clinical significance of these mechanisms is most clearly manifested in the cerebral vasculature, where even minor thrombotic or microcirculatory changes lead to severe and often irreversible consequences. Therefore, the following discussion focuses on cerebrovascular and cardiovascular disorders in antiphospholipid syndrome, which represent one of the leading clinical phenotypes of the disease, determine patient prognosis, and at the same time reflect the key pathogenetic principles characteristic of systemic vascular pathology in antiphospholipid syndrome.

Ischemic stroke is one of the most common and clinically significant arterial manifestations of antiphospholipid syndrome and occupies a leading position in the spectrum of its cerebrovascular complications [36]. According to large prospective and multicenter studies, stroke accounts for a substantial proportion of arterial thromboses in antiphospholipid syndrome and is often the first manifestation of the disease, which determines its high diagnostic and prognostic significance. Particular attention is drawn to the association of antiphospholipid syndrome with ischemic stroke at a young age, when traditional vascular risk factors are often absent or minimally expressed [4]. A systematic review examining the prevalence of antiphospholipid antibodies in young adults with cerebrovascular disorders showed that antiphospholipid antibodies are detected in a substantial proportion of patients with ischemic stroke or transient ischemic attacks, at rates significantly higher than those observed in the general population [37], which confirms the role of antiphospholipid syndrome as one of the leading non-traditional risk factors for stroke in young individuals.

The association between antiphospholipid antibodies and ischemic stroke in young patients has been demonstrated in classical neuroepidemiological studies, in which the presence of antiphospholipid and/or anticardiolipin antibodies correlated with an increased risk of cerebral ischemia [38]. Moreover, this association is independent of traditional vascular risk factors, which emphasizes the pathogenetic specificity of antiphospholipid syndrome [36].

A distinct characteristic of the cerebrovascular manifestations of antiphospholipid syndrome is the tendency toward recurrent ischemic stroke. Prospective observations and analyses of risk factors for recurrent thrombosis indicate that in patients with antiphospholipid syndrome, the risk of recurrent arterial thrombotic complications remains elevated even during standard antithrombotic therapy [39]. This is consistent with the concept of a persistent immunopathogenetic imbalance that is not completely eliminated even when the coagulation cascade is controlled.

An important aspect of stroke risk in antiphospholipid syndrome is the patients' serological profile. Studies have shown that the presence of antiphospholipid antibodies, as well as positivity for multiple types of these antibodies, correlates with a higher likelihood of arterial thrombotic complications, including ischemic stroke [40]. High-risk serological profiles are considered a tool for the stratification of patients with cerebrovascular manifestations of antiphospholipid syndrome.

Transient ischemic attacks are also an important, although often underestimated, component of the

spectrum of cerebrovascular manifestations of antiphospholipid syndrome and are regarded as one of the forms of its arterial manifestation. In clinical series and review articles, transient ischemic attacks are described as a common initial manifestation of cerebrovascular involvement in antiphospholipid syndrome, preceding the development of a full-blown ischemic stroke [24].

Available data indicate that transient ischemic attacks in antiphospholipid syndrome are not incidental but reflect the same immune-thrombotic mechanism that underlies ischemic stroke. In a systematic review examining the prevalence of antiphospholipid antibodies in young patients with cerebrovascular manifestations, transient ischemic attacks were considered together with ischemic stroke as part of a single pathological continuum, confirming their common pathogenetic basis [41].

The particular significance of transient ischemic attacks in antiphospholipid syndrome lies in their prognostic role. Accumulated data indicate that transient ischemic attacks in patients with antiphospholipid syndrome may serve as predictors of subsequent cerebrovascular manifestations, particularly ischemic stroke [1, 4, 34]. Such a sequence of events is consistent with the concept of persistent vascular activation and chronic immune-coagulation imbalance characteristic of antiphospholipid syndrome.

From a pathogenetic perspective, transient ischemic attacks in antiphospholipid syndrome should not be regarded as a «mild» or clinically insignificant form of cerebrovascular pathology. On the contrary, their occurrence reflects temporary but recurrent ischemia caused by activation of the endothelium, platelets, and the coagulation cascade involving antiphospholipid antibodies. Thus, transient ischemic attacks are a manifestation of the same systemic process that, if it progresses further or is inadequately controlled, may lead to irreversible ischemic damage to brain tissue.

Thus, cerebrovascular disorders in antiphospholipid syndrome should be regarded not as an isolated chain of thrombotic manifestations but as one of the clinical manifestations of a systemic immune-thrombotic process that develops against the background of the persistent effects of antiphospholipid antibodies [44]. In the presence of a common immunological background, the brain represents a particularly vulnerable target due to the combination of its high metabolic sensitivity, the complex organization of the microcirculatory bed, and the limited compensatory capacity of the cerebral circulation.

Importantly, the development of cerebrovascular disorders in antiphospholipid syndrome is not limited to a single pathogenetic mechanism. Within a unified systemic process, both arterial thrombotic manifestations in the cerebral vascular bed and cardioembolic mechanisms associated with valvular involvement or intracardiac thrombus formation, as well as microvascular forms of brain injury, may develop [40]. The described variability in the pathways of ischemia does not contradict the thrombotic nature of antiphospholipid syndrome but, on the contrary, emphasizes its multifocal and systemic nature.

Particular attention in this context should be paid to the microvascular component, which reflects the ability of antiphospholipid syndrome to manifest at the level of the cerebral microcirculation even in the absence of large-vessel occlusion. Thus, microcirculatory and microperfusion disturbances are regarded as a functional continuation of systemic immune-endothelial activation and may determine both subclinical and clinically significant manifestations of cerebrovascular dysfunction [45, 46].

Cerebrovascular disorders in antiphospholipid syndrome should be regarded not as localized involvement of an individual vascular bed but as one of the clinical manifestations of systemic vascular pathology caused by the persistent effects of antiphospholipid antibodies. Arterial thrombosis, microvascular lesions, and cardioembolic mechanisms underlying stroke and transient ischemic attacks are simultaneously involved in the development of cardiac and pulmonary vascular complications. In this context, the analysis of cardiovascular manifestations of antiphospholipid syndrome is essential for a comprehensive understanding of the systemic nature of the syndrome and the relationship between cerebral and cardiac vascular complications.

Antiphospholipid syndrome is associated with a broad spectrum of cardiovascular lesions involving both arterial and venous vascular beds, as well as cardiac structures. Cardiovascular manifestations of antiphospholipid syndrome are not limited exclusively to the consequences of classical thrombus formation but develop as a result of the aforementioned combination of immune-mediated endothelial activation, a prothrombotic state, and chronic vascular inflammation, leading to involvement of the coronary arteries, valvular apparatus, pulmonary vasculature, and intracardiac structures [47, 48].

Arterial thromboses are among the cardiovascular manifestations of antiphospholipid syndrome. They predominantly include coronary artery involvement with the development of ischemic heart disease. Coronary manifestations in antiphospholipid syndrome often occur in patients without classical risk factors for atherosclerosis, which emphasizes the independent role of immune mechanisms in the pathogenesis of coronary vascular involvement [49, 50]. In such cases,

coronary artery thrombosis may occur in the presence of minimal or even absent atherosclerotic changes, which distinguishes antiphospholipid syndrome from classical atherothrombotic ischemic heart disease [51].

Myocardial infarction is another clinically significant, although relatively rare, manifestation of antiphospholipid syndrome and is of particular importance in young patients. Data from the RATIO study convincingly demonstrated that the presence of antiphospholipid antibodies is significantly associated with an increased risk of myocardial infarction in young women, independently of traditional cardiovascular risk factors [52]. In the large prospective Euro-Phospholipid Project, myocardial infarction was documented as one of the major arterial manifestations in patients with confirmed antiphospholipid syndrome and was associated with increased mortality [2].

Venous thromboses are the most common form of vascular involvement in antiphospholipid syndrome and include deep vein thrombosis and pulmonary embolism. Venous thrombus formation in antiphospholipid syndrome is caused by a combination of a hypercoagulable state, endothelial and platelet activation, and impaired fibrinolysis, which distinguishes this syndrome from isolated inherited thrombophilias [53]. In turn, pulmonary embolism may be either a primary manifestation of antiphospholipid syndrome or a consequence of recurrent venous thrombosis, providing a basis for the subsequent development of pulmonary vascular complications [54].

Pulmonary hypertension occupies a special place among the cardiovascular manifestations of antiphospholipid syndrome and may develop as a result of chronic thromboembolic obstruction of the pulmonary arteries or microvascular thrombotic lesions of the pulmonary vascular bed [55]. Systematic reviews indicate that pulmonary hypertension in antiphospholipid syndrome is an underestimated complication and often has a progressive course, which significantly worsens patient prognosis [56, 57]. Importantly, antiphospholipid antibodies may serve as an independent risk marker for the development of pulmonary hypertension even in the absence of clinically apparent episodes of acute pulmonary embolism.

Valvular heart lesions are a characteristic, although often subclinical, feature of antiphospholipid syndrome. The most typical morphological variant is nonbacterial thrombotic endocarditis (Libman-Sacks endocarditis), which manifests as leaflet thickening, vegetations, and varying degrees of regurgitation [58, 59] Such lesions are associated with the persistent presence of antiphospholipid antibodies and may serve as a source of cardioembolic complications, including cerebral ones. Thus, echocardiographic studies indicate that valvular changes in antiphospholipid syndrome often progress over time, even in the absence of an infectious process [60].

At the same time, current research increasingly emphasizes the reconsideration of the reproductive manifestations of antiphospholipid syndrome as a distinct clinical and pathogenetic phenotype that reflects the systemic nature of immunothrombosis and determines the course of pregnancy and perinatal outcomes [11]. Reproductive manifestations of antiphospholipid syndrome have independent clinical significance and at the same time reflect the systemic nature of the disease. They occur in women of reproductive age, form a significant proportion of perinatal complications and losses and form a significant medical and social burden due to miscarriage, preeclampsia, fetal growth retardation and premature birth [6] Epidemiologically, placental-mediated complications predominate among the obstetric manifestations of antiphospholipid syndrome [5]. Thus, according to the EUROAPS registry, among 1 000 cases of antiphospholipid syndrome in pregnant women, the rate of miscarriage was approximately 38.6%, early preeclampsia 18.1%, and early fetal growth restriction 16.1%. Placental dysfunction is the pathophysiological basis of these manifestations [61]. At the same time, clinical data on the insufficient efficacy of standard antithrombotic prophylaxis (low-dose acetylsalicylic acid in combination with low-molecular-weight heparin) indicate that perinatal complications in antiphospholipid syndrome «are not limited to «classical» thrombosis but develop through a more complex cascade of immune-inflammatory-coagulation reactions» [62, 63].

In current studies of pathogenesis, the concept of «placental immunothrombosis» is gaining increasing support, defining the reproductive manifestations of antiphospholipid syndrome as a tissue-specific phenotype of systemic immunothrombosis. In this model, the placenta is regarded as a target organ characterized by unique processes of trophoblast invasion, spiral artery remodeling, and the need to maintain a delicate immune tolerance within the «mother-placenta-fetus» system [26, 64]. The initial trigger is the interaction of antiphospholipid antibodies, primarily anti-β2GPI antibodies, with the trophoblast and endothelium, which initiates cellular activation, impairs the invasive and differentiation potential of the trophoblast, and contributes to impaired placental development even before the establishment of mature placental perfusion [30]. Placental dysfunction and its associated clinical manifestations (early or severe preeclampsia, fetal growth restriction, and preterm birth) are not «late» consequences of incidental thrombosis but

rather expected outcomes of early placentation failure, exacerbated by a local thrombo-inflammatory microenvironment [65]. Subsequently, the link between autoimmune activation and coagulation within the placenta is mediated by the complement system. In antiphospholipid syndrome, complement is not merely a marker but an effector of injury and the C5a fragment is capable of inducing the recruitment and activation of innate immune cells and enhancing tissue factor expression, thereby shifting the balance toward a procoagulant state [31, 66]. In parallel, neutrophil activation occurs with the formation of «neutrophil extracellular traps» (NETs), which link inflammatory and coagulation mechanisms by damaging the trophoblast and promoting microthrombosis. These structures consist of networks of extracellular DNA associated with proteases, are formed by activated neutrophils, damage the endothelium and trophoblast, and provide a matrix for microthrombus formation, thereby linking inflammatory and coagulation mechanisms within the placental circulation [67]. Collectively, these processes sustain endothelial dysfunction, microvascular perfusion disturbances, and microthrombosis, which are of particular clinical significance in the placenta, since even moderate changes in microcirculation may result in significant hypoxia and fetoplacental insufficiency [26]. Thus, individual clinical manifestations of the obstetric phenotype of antiphospholipid syndrome reflect different aspects of a unified immunothrombotic cascade. Early reproductive complications are associated primarily with impaired implantation and trophoblast invasion, preeclampsia with endothelial dysfunction and complement-mediated inflammation, while fetal growth restriction and preterm birth result from chronic placental insufficiency caused by microthrombosis and impaired placental perfusion. Epidemiological data are additionally consistent with this model: positivity for antiphospholipid antibodies is associated with an increased risk of fetal growth restriction, reflecting the placenta-mediated nature of a substantial proportion of perinatal complications [68].

The described concept most consistently explains the limitations of antithrombotic prophylaxis. If primary trophoblast injury, complement-dependent inflammation, and cytotoxicity associated with the formation of NETs develop during the early stages of placentation, then anticoagulation, while reducing the risk of thrombosis, is not always capable of neutralizing the immune-inflammatory mechanisms underlying impaired placentation and subsequent placental insufficiency [26, 63]. Clinical data indicate that even with standard prophylactic therapy, the risk of complications remains elevated in patients with an unfavorable antiphospholipid antibody profile, particularly in the presence of lupus anticoagulant, anticardiolipin antibodies, and anti-β2GPI antibodies. According to the results of the PREGNANTS study, this group showed a reduced live birth rate (to approximately 30%) and increased rates of preeclampsia, fetal growth restriction, and stillbirth [69]. In this case, targeted modulation of the effector mechanisms of immunothrombosis appears promising. For example, experimental data demonstrate that hydroxychloroquine may prevent complement-dependent placental and fetal injury by reducing C5a levels without altering antibody titers. This study supports the hypothesis that a combined effect on coagulation and immune-inflammatory mechanisms is necessary [70].

Clinically, these mechanisms manifest as characteristic complications reflecting different stages and components of impaired placental function. In particular, individual clinical manifestations develop as a consequence of the predominance of specific components of the immunothrombotic cascade. Thus, early pregnancy loss in antiphospholipid syndrome results from impaired implantation and early placentation caused by the interaction of antiphospholipid antibodies with the trophoblast. Anti-β2GPI antibodies inhibit the invasive capacity of the trophoblast, impair its proliferation and differentiation, and promote local complement activation, leading to cellular injury during the early stages of placental development [11]. As a result, adequate implantation and early uteroplacental blood flow fail to develop, clinically manifesting as recurrent miscarriages [65].

Preeclampsia in antiphospholipid syndrome results from systemic and local endothelial dysfunction that develops under the influence of complement-dependent inflammation and immunothrombosis. Complement activation, particularly the generation of C5a, induces the expression of tissue factor CD142, endothelial activation, and neutrophil recruitment, thereby promoting the activation of inflammatory and coagulation mechanisms [64, 71]. Impaired spiral artery remodeling and reduced placental perfusion, in turn, lead to the development of hypoxia, the release of antiangiogenic factors, and the development of the clinical picture of preeclampsia, which is often early-onset and severe [3, 72].

Fetal growth restriction in antiphospholipid syndrome is a direct consequence of chronic placental dysfunction that develops in the setting of impaired blood flow in small vessels and immunothrombotic processes within the placenta. As a result, microthrombosis, cellular injury, and endothelial dysfunction reduce the efficiency of oxygen and nutrient transport, leading to chronic fetal hypoxia. At the same time, defective trans-

formation of the spiral arteries reduces the adaptive capacity of placental blood flow, clinically manifesting as fetal growth restriction [73].

Preterm birth is also mentioned among the complications; however, it is predominantly iatrogenic and results from severe placenta-mediated complications, particularly preeclampsia or fetal growth restriction. Progressive placental insufficiency, inflammatory-coagulation activation, and deterioration of fetal condition necessitate early delivery to reduce the risk of perinatal complications. In some cases, local inflammation and activation of innate immunity play an additional role and may contribute to the premature onset of labor [74].

Stillbirth in antiphospholipid syndrome is also associated with severe placental insufficiency, extensive microthrombosis, and impaired fetoplacental circulation. Complement-mediated injury, activation of NETs, and persistent placental hypoperfusion play a major role in the pathogenesis, leading to fetal hypoxia [69, 75]. These processes reflect the most severe degree of placental dysfunction in antiphospholipid syndrome. Thus, as mentioned above, the reproductive manifestations of antiphospholipid syndrome represent a tissue-specific manifestation of systemic immunothrombosis at the placental level, where the interaction of immune, inflammatory, and coagulation mechanisms leads to the development of placental dysfunction and associated perinatal complications.

Isolated cases of antiphospholipid syndrome associated with peripartum cardiomyopathy have also been described in the literature [76]. It has been suggested that endothelial dysfunction, microvascular thrombosis, and the hypercoagulable state characteristic of antiphospholipid syndrome may contribute to the development of myocardial dysfunction in the postpartum period.

Of fundamental importance for a comprehensive understanding of antiphospholipid syndrome is the recognition of the common vascular mechanisms underlying lesions of the brain, heart, and placenta. In all these vascular beds, a universal pathogenetic scenario is repeated: the effects of antiphospholipid antibodies, endothelial activation, involvement of platelets and complement, formation of a proinflammatory microenvironment, and development of thrombotic and microcirculatory disturbances. At the same time, the differences between cerebrovascular, cardiac, and obstetric manifestations of antiphospholipid syndrome are determined not so much by differences in the nature of the pathological process as by the characteristics of the local vascular bed and organ-specific susceptibility to ischemia [76].

However, it should once again be emphasized that antiphospholipid syndrome is a systemic vascular-immune nosological entity in which clinical manifestations are not limited to large arterial or venous thromboses. Along with cerebrovascular, cardiac, and obstetric disorders, a broad spectrum of other systemic manifestations is observed in antiphospholipid syndrome, reflecting the generalized nature of endothelial dysfunction, microvascular thrombus formation, and chronic inflammation [77].

For example, neurological complications in antiphospholipid syndrome extend beyond ischemic stroke and transient ischemic attacks and may also include cognitive impairment, headache, epileptic seizures, and other manifestations of central nervous system dysfunction resulting from a combination of recurrent microischemic events, chronic disturbances of cerebral microcirculation, and the direct immune-mediated effects of antiphospholipid antibodies on cerebral microcirculation [44, 78]. The presence of such manifestations is associated with a more severe course of the disease and an increased risk of future thrombotic complications.

Renal involvement in antiphospholipid syndrome, collectively referred to as antiphospholipid nephropathy, is a characteristic example of organ-specific microvascular pathology. It includes thrombotic lesions of intrarenal arterioles and capillaries, leading to arterial hypertension, proteinuria, and progressive decline in renal function [79]. Antiphospholipid nephropathy is regarded as a marker of systemic microangiopathy and correlates with high cardiovascular risk, particularly with the incidence of arterial thrombosis [80, 81].

Cutaneous manifestations, such as livedo reticularis, livedo racemosa, ulcerative lesions, and necrosis, are among the earliest and most visually apparent signs of systemic vascular involvement in antiphospholipid syndrome. They reflect impaired microcirculation and thrombosis of small cutaneous vessels and are often associated with central nervous system or renal involvement, underscoring their prognostic value [1].

Hematological manifestations, primarily thrombocytopenia, are a common finding in antiphospholipid syndrome and have a complex pathogenetic basis. Despite the reduced platelet count, thrombocytopenia in antiphospholipid syndrome does not reduce the risk of thrombosis but, on the contrary, is often associated with an increased thrombotic risk, reflecting the paradoxical combination of immune-mediated platelet destruction and platelet activation [82]. The presence of hematological abnormalities is regarded as an additional marker of systemic disease activity.

An important conceptual aspect is the relationship between these systemic lesions and the risk of cardio-

vascular complications. Neurological, renal, cutaneous, and hematological manifestations are not isolated phenomena but develop against a common immunopathogenetic background with arterial and venous thromboses. Their presence indicates generalized involvement of the vascular endothelium and microcirculation and should be regarded as a factor associated with an unfavorable prognosis for the development of severe cardiovascular complications.

CONCLUSIONS

Antiphospholipid syndrome emerges as a systemic immune-vascular nosological entity in which cerebrovascular and cardiovascular manifestations constitute the main clinical phenotype and determine the long-term prognosis of the disease. Understanding antiphospholipid syndrome as a unified immune-coagulation process is of fundamental importance for clinical practice, as it provides a basis for more accurate risk stratification, early identification of patients with a high probability of severe vascular complications, and the development of pathogenetically substantiated therapeutic methods targeting not only the coagulation cascade but also the immune and inflammatory components of the disease. Such an integrative approach is fundamental to optimizing treatment and improving the prognosis of patients with antiphospholipid syndrome.

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CONFLICT OF INTERESTS

The Authors declare no conflict of interest

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